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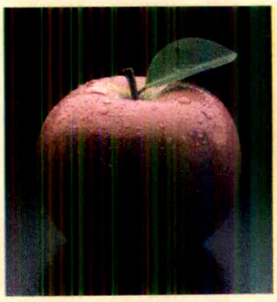
Once for prophylaxis. Once daily for cure.

The prophylactic dose of ROCEPHIN is also the daily therapeutic dose. ROCEPHIN, 1 gm given once prior to surgery,* provides effective prophylaxis against infection and is on board throughout the perioperative period—even if surgery is delayed or prolonged.

And ROCEPHIN, 1 gm given once a day, is the therapeutic dosage for the following common postsurgical infections: respiratory tract or skin/skin structure infections due to *Staphylococcus aureus, Klebsiella pneumoniae* and *Proteus mirabilis;* urinary tract infections due to *Escherichia coli, K. pneumoniae* and *P. mirabilis.*

Efficacy, economy and ease. ROCEPHIN: 1 gm once for prophylaxis, once daily for cure.

P 24,994



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ceftriaxone sodium/Roche

As with any cephalosporin, there exists the possibility of hypersensitivity reactions, especially in individuals with a history of sensitivity.

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*In contaminated or potentially contaminated procedures (*e.g.,* vaginal or abdominal hysterectomy), and for patients in whom infection at the operative site would present serious risk (*e.g.,* coronary artery bypass graft [CABG] surgery).

Please see adjacent page for summary of product information.

Vol. 125

ROCEPHIN® (ceftriaxone sodium/Roche)

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE: Rocephin is indicated for the treatment of the following infections when caused by susceptible organisms:

LOWER RESPIRATORY TRACT INFECTIONS caused by *Strep. pneumoniae, Streptococcus* species (excluding enterococci), *Staph. aureus, H. influenzae, H. parainfluenzae, Klebsiella* species (including *K. pneumoniae*), *E. coli, E. aerogenes, Proteus mirabilis* and *Serratia marcescens.*

SKIN AND SKIN STRUCTURE INFECTIONS caused by *Staph. aureus, Staph. epidermidis, Streptococcus* species (excluding enterococci), *E. cloacae, Klebsiella* species (including *K. pneumoniae*), *Proteus mirabilis* and *Pseudomonas aeruginosa.*

URINARY TRACT INFECTIONS (complicated and uncomplicated) caused by *E. coli, Proteus mirabilis, Proteus vulgaris, M. morganii* and *Klebsiella* species (including *K. pneumoniae*).

UNCOMPLICATED GONORRHEA (cervical/urethral and rectal) caused by *Neisseria gonorrhoeae*, including both penicillinase and nonpenicillinase producing strains.

PELVIC INFLAMMATORY DISEASE caused by *N. gonorrhoeae.*

BACTERIAL SEPTICEMIA caused by *Staph. aureus, Strep. pneumoniae, E. coli, H. influenzae* and *K. pneumoniae.*

BONE AND JOINT INFECTIONS caused by *Staph. aureus, Strep. pneumoniae Streptococcus* species (excluding enterococci), *E. coli, P. mirabilis, K. pneumoniae* and *Enterobacter* species.

INTRA-ABDOMINAL INFECTIONS caused by *E. coli* and *K. pneumoniae.*

MENINGITIS caused by *H. influenzae, N meningitidis* and *Strep. pneumoniae.* Ceftriaxone has also been used successfully in a limited number of cases of meningitis and shunt infections caused by *Staph. epidermidis* and *E. coli.*

SURGICAL PROPHYLAXIS: Preoperative administration of a single 1 gm dose may reduce incidence of postoperative infections in patients undergoing surgical procedures classified as contaminated or potentially contaminated (*e.g.*, vaginal or abdominal hysterectomy) and in those for whom infection at the operative site presents serious risk (*e.g.*, during coronary artery bypass surgery).

Although ceftriaxone has been shown to have been as effective as cefazolin in the prevention of infection following coronary artery bypass surgery, no placebo-controlled trials have been conducted to evaluate any cephalosporin antibiotic in the prevention of infection following coronary artery bypass surgery. When administered before indicated surgical procedures, a single 1 gm dose provides protection from most infections due to susceptible organisms for duration of procedure.

SUSCEPTIBILITY TESTING: Before instituting treatment with Rocephin, appropriate specimens should be obtained for isolation of the causative organism and for determination of its susceptibility to the drug. Therapy may be instituted prior to obtaining results of susceptibility testing.

CONTRAINDICATIONS: Rocephin is contraindicated in patients with known allergy to the cephalosporin class of antibiotics.

WARNINGS: BEFORE THERAPY WITH ROCEPHIN IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis, reported with nearly all antibacterial agents, including ceftriaxone, may range in severity from mild to life-threatening. Therefore, consider this diagnosis in patients who present with diarrhea subsequent to administration of antibacterial agents.

Treatment with antibacterial agents alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After establishing diagnosis of pseudomembranous colitis, initiate therapeutic measures. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consider management with fluids and electrolytes, protein supplementation and treatment with an oral antibacterial drug effective against *C. difficile*.

PRECAUTIONS: *GENERAL:* Although transient elevations of BUN and serum creatinine have been observed, at the recommended dosages, the nephrotoxic potential of Rocephin is similar to that of other cephalosporins.

Ceftriaxone is excreted via both biliary and renal excretion (see Clinical Pharmacology). Therefore, patients with renal failure normally require no adjustment in dosage when usual doses of Rocephin are administered, but concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

Dosage adjustments should not be necessary in patients with hepatic dysfunction; however, in patients with both hepatic dysfunction and significant renal disease, Rocephin dosage should not exceed 2 gm daily without close monitoring of serum concentrations.

Alterations in prothrombin times have occurred rarely in patients treated with Rocephin. Patients with impaired vitamin K synthesis or low vitamin K stores (*e.g.*, chronic hepatic disease and malnutrition) may require monitoring of prothrombin time during Rocephin treatment. Vitamin K administration (10 mg weekly) may be necessary if the prothrombin time is prolonged before or during therapy.

Prolonged use of Rocephin may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Rocephin should be prescribed with caution in individuals with a history of gastrointestinal disease, especially colitis.

Rare cases reported of sonographic abnormalities seen in the gallbladder; patients may also have symptoms of gallbladder disease. These abnormalities, variously described as sludge precipitations, echoes with shadows, may be misinterpreted as concretions. Chemical nature of sonographically-detected material not determined. Condition appears to be transient and reversible upon discontinuation of Rocephin and conservative management. Therefore, discontinue Rocephin if signs and symptoms suggestive of gallbladder disease and/or the sonographic findings described above develop.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Carcinogenesis: Considering the maximum duration of treatment and the class of the compound, carcinogenicity studies with ceftriaxone in animals have not been performed. The maximum duration of animal toxicity studies was six months.

Mutagenesis: Genetic toxicology tests included the Ames test, a micronucleus test and a test for chromosomal aberrations in human lymphocytes cultured *in vitro* with ceftriaxone. Ceftriaxone showed no potential for mutagenic activity in these studies.

Impairment of Fertility: Ceftriaxone produced no impairment of fertility when given intravenously to rats at daily doses up to 586 mg/kg/day, approximately 20 times the recommended clinical dose of 2 gm/day.

REGNANCY: Teratogenic Effects: Pregnancy Category B. Reproductive studies have been per-
ned in mice and rats at doses up to 20 times the usual human dose and have no evidence of
yotoxicity, fetotoxicity or teratogenicity. In primates, no embryotoxicity or teratogenicity was
nstrated at a dose approximately three times the human dose.

are, however, no adequate and well-controlled studies in pregnant women. Because animal
uctive studies are not always predictive of human response, this drug should be used dur-
gnancy only if clearly needed.

[illegible]dium/Roche)

Nonte[illegible]ffects: In rats, in the Segment I (fertility and general reproduction) and Segment III (perinatal and postnatal) studies with intravenously administered ceftriaxone, no adverse effects were noted on various reproductive parameters during gestation and lactation, including postnatal growth, functional behavior and reproductive ability of the offspring, at doses of 586 mg/kg/day or less.

NURSING MOTHERS: Low concentrations of ceftriaxone are excreted in human milk. Caution should be exercised when Rocephin is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness of Rocephin in neonates, infants and children have been established for the dosages described in the Dosage and Administration section. *In vitro* studies have shown ceftriaxone, like some other cephalosporins, can displace bilirubin from serum albumin. Rocephin should not be administered to hyperbilirubinemic neonates, especially prematures.

ADVERSE REACTIONS: Rocephin is generally well tolerated. In clinical trials, the following adverse reactions, which were considered to be related to Rocephin therapy or of uncertain etiology, were observed:

LOCAL REACTIONS—pain, induration or tenderness at the site of injection (1%). Less frequently reported (less than 1%) was phlebitis after I.V. administration.

HYPERSENSITIVITY—rash (1.7%). Less frequently reported (less than 1%) were pruritus, fever or chills.

HEMATOLOGIC—eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolongation of the prothrombin time.

GASTROINTESTINAL—diarrhea (2.7%). Less frequently reported (less than 1%) were nausea or vomiting, and dysgeusia. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS).

HEPATIC—elevations of SGOT (3.1%) or SGPT (3.3%). Less frequently reported (less than 1%) were elevations of alkaline phosphatase and bilirubin.

RENAL—elevations of the BUN (1.2%). Less frequently reported (less than 1%) were elevations of creatinine and the presence of casts in the urine.

CENTRAL NERVOUS SYSTEM—headache or dizziness were reported occasionally (less than 1%).

GENITOURINARY—moniliasis or vaginitis were reported occasionally (less than 1%).

MISCELLANEOUS—diaphoresis and flushing were reported occasionally (less than 1%).

Other rarely observed adverse reactions (less than 0.1%) include leukocytosis, lymphocytosis, monocytosis, basophilia, a decrease in the prothrombin time, jaundice, gallbladder sludge, glycosuria, hematuria, anaphylaxis, bronchospasm, serum sickness, abdominal pain, colitis, flatulence, dyspepsia, palpitations and epistaxis.

DOSAGE AND ADMINISTRATION: Rocephin may be administered intravenously or intramuscularly. The usual adult daily dose is 1 to 2 gm given once a day (or in equally divided doses twice a day) depending on the type and severity of the infection. The total daily dose should not exceed 4 grams.

For the treatment of serious miscellaneous infections in children, other than meningitis, the recommended total daily dose is 50 to 75 mg/kg (not to exceed 2 grams), given in divided doses every 12 hours.

Generally, Rocephin therapy should be continued for at least two days after the signs and symptoms of infection have disappeared. The usual duration is 4 to 14 days; in complicated infections longer therapy may be required.

In the treatment of meningitis, a daily dose of 100 mg/kg (not to exceed 4 grams), given in divided doses every 12 hours, should be administered with or without a loading dose of 75 mg/kg.

For the treatment of uncomplicated gonococcal infections, a single intramuscular dose of 250 mg is recommended.

For preoperative use (surgical prophylaxis), a single dose of 1 gm administered 1/2 to 2 hours before surgery is recommended.

When treating infections caused by *Streptococcus pyogenes*, therapy should be continued for at least ten days.

No dosage adjustment is necessary for patients with impairment of renal or hepatic function; however, blood levels should be monitored in patients with severe renal impairment (*e.g.*, dialysis patients) and in patients with both renal and hepatic dysfunctions.

HOW SUPPLIED: Rocephin (ceftriaxone sodium/Roche) is supplied as a sterile crystalline powder in glass vials and piggyback bottles. The following packages are available:

Vials containing 250 mg, 500 mg, 1 gm or 2 gm equivalent of ceftriaxone; piggyback bottles containing 1 gm or 2 gm equivalent of ceftriaxone; bulk pharmacy containers containing 10 gm equivalent of ceftriaxone (NOT FOR DIRECT ADMINISTRATION).

Also supplied as a sterile crystalline powder as follows:
ADD-Vantage Vials®* containing 1 gm or 2 gm equivalent of ceftriaxone.

Also supplied premixed as a frozen iso-osmotic, sterile, nonpyrogenic solution of ceftriaxone sodium in 50 mL single dose plastic containers,† as follows:

1 gm equivalent of ceftriaxone, iso-osmotic with approximately 1.9 gm dextrose hydrous, USP added.

2 gm equivalent of ceftriaxone, iso-osmotic with approximately 1.2 gm dextrose hydrous, USP added.

NOTE: Rocephin in the frozen state should not be stored above -20°C.

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†Manufactured for Roche Laboratories, a division of Hoffmann-La Roche Inc., by Travenol Laboratories, Inc., Deerfield, Illinois 60015.

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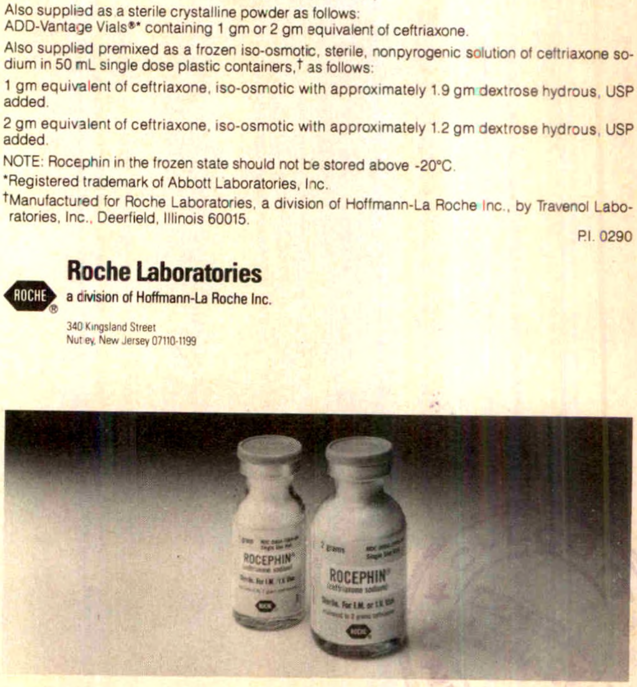

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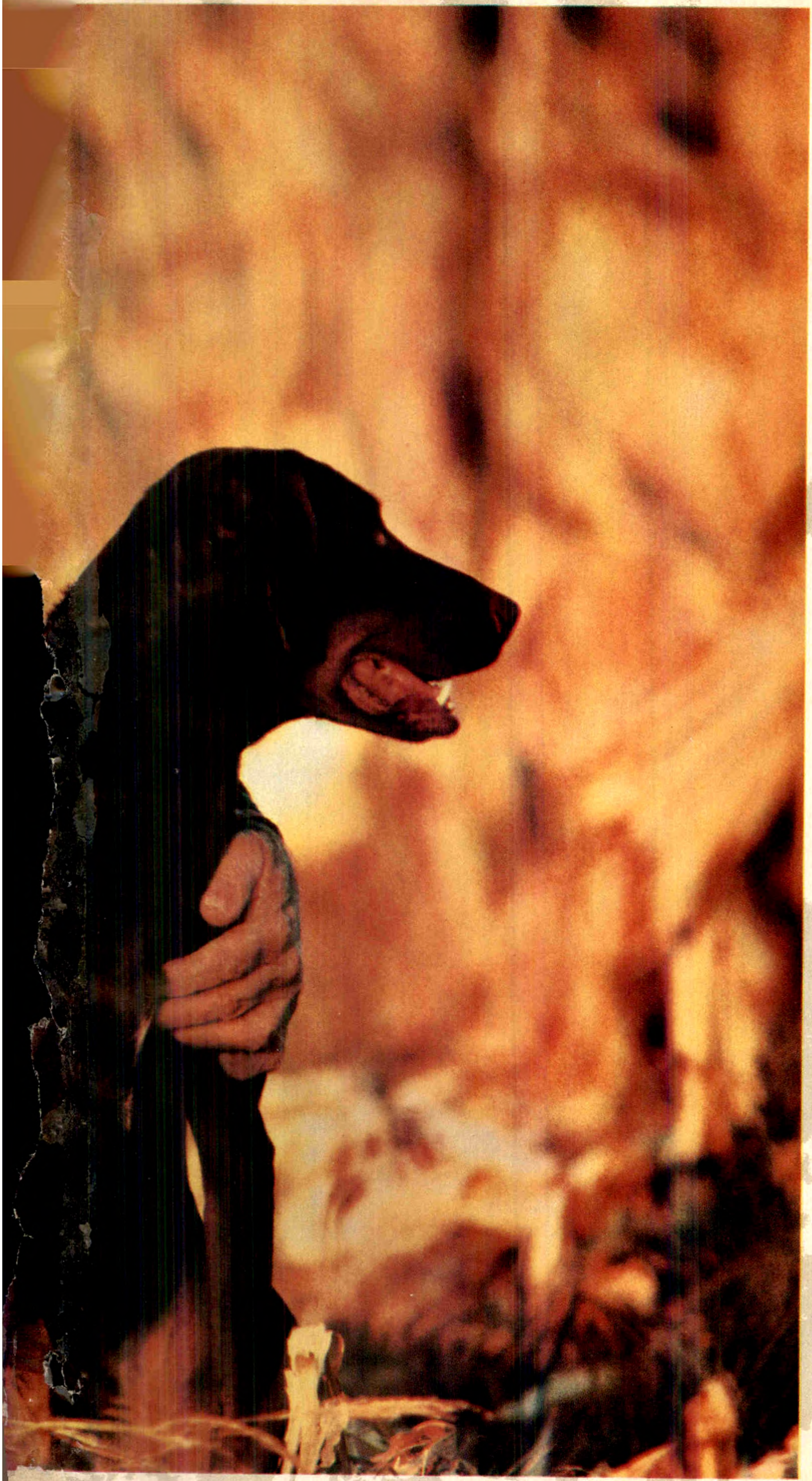

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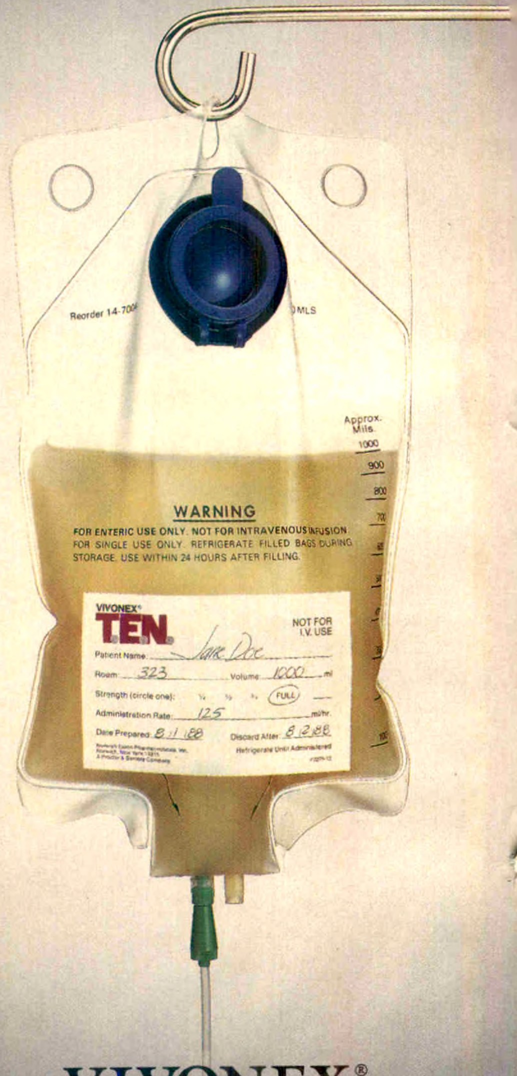
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References: **1.** Andrassy RJ: Preserving the gut mucosal barrier and enhancing immune response. *Contemp Surg* 1988;32(2-A):21-27. **2.** Hoover HC Jr: Enteral elemental nutrition in major abdominal surgery. *Contemp Surg* 1986;28(4-A):12-17. **3.** Bower RH, Talamini MA, Sax HC, et al: Postoperative enteral vs parenteral nutrition: A randomized controlled trial. *Arch Surg* 1986; 121:1040-1045. **4.** Souba WW, Smith RJ, Wilmore DW: Glutamine metabolism by the intestinal tract. *JPEN* 1985;9:608-617. **5.** Fox AD, Kripke SA, Berman JR, et al: Reduction of the severity of enterocolitis by glutamine-supplemented enteral diets. *Surgical Forum* 1987;38:43-44. **6.** Hwang TL, O'Dwyer ST, Smith RJ: Preservation of small bowel mucosa using glutamine-enriched parenteral nutrition. *Surgical Forum* 1986;37:56-57.

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Claude H. Organ, Jr, MD, Oakland, Calif

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- Computerized EEG is a dependable criterion for selective shunting and for shunt patency confirmation during carotid endarterectomy.

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Invited Commentary: John A. Collins, MD, Stanford, Calif

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Instructions for Authors . . . . . **See April 1990 issue, p 529**

DISCHARGE

INTRAVENOUS

PRIMAXIN

(Imipenem-Cilastatin Sodium|MSD

A SUCCESSFUL TREATMENT OUTCOME
FOR MANY PATIENTS*

*In one study, 90% of 135 patients with clinical signs of infection and two positive blood cultures were cured or improved (66% Cured, 24% Improved). Eron, L. J.: Imipenem/cilastatin therapy of bacteremia, Am. J. Med. *78(Suppl. 6A)*: 95-99, June 7, 1985.

PRIMAXIN is contraindicated in patients who have shown hypersensitivity to any component of this product. Before initiating therapy with PRIMAXIN, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, other beta-lactams, and other allergens. If an allergic reaction to PRIMAXIN occurs, discontinue the drug. Serious hypersensitivity reactions may require epinephrine and other emergency measures.

Please see Brief Summary of Prescribing Information.

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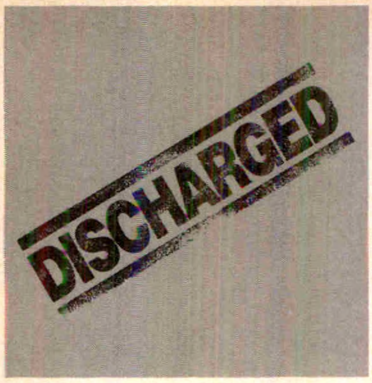

A SUCCESSFUL TREATMENT OUTCOME FOR MANY PATIENTS*

INTRAVENOUS

PRIMAXIN®

(Imipenem-Cilastatin Sodium/MSD)

*In one study, 90% of 135 patients with clinical signs of infection and two positive blood cultures were cured or improved (66% Cured, 24% Improved). Eron, L. J.: Imipenem/cilastatin therapy of bacteremia, Am. J. Med. *78(Suppl. 6A)*: 95-99, June 7, 1985.

Contraindications: PRIMAXIN® (Imipenem-Cilastatin Sodium, MSD) is contraindicated in patients who have shown hypersensitivity to any component of this product.

Warnings: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (anaphylactic) REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH BETA LACTAMS. THESE REACTIONS ARE MORE APT TO OCCUR IN PERSONS WITH A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS.

THERE HAVE BEEN REPORTS OF PATIENTS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE HYPERSENSITIVITY REACTIONS WHEN TREATED WITH ANOTHER BETA LACTAM. BEFORE INITIATING THERAPY WITH 'PRIMAXIN,' CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OTHER BETA LACTAMS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION TO 'PRIMAXIN' OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with virtually all antibiotics, including PRIMAXIN; therefore it is important to consider its diagnosis in patients who develop diarrhea in association with antibiotic use. This colitis may range in severity from mild to life threatening.

Mild cases of pseudomembranous colitis may respond to drug discontinuance alone. In more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte, and protein supplementation, and the use of a drug such as oral vancomycin, as indicated. Isolation of the patient may be advisable. Other causes of colitis should also be considered.

Precautions: *General* – CNS adverse experiences such as confusional states, myoclonic activity, and seizures have been reported during treatment with PRIMAXIN, especially when recommended dosages were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function. However, there have been reports of CNS adverse experiences in patients who had no recognized or documented underlying CNS disorder or compromised renal function.

Patients with severe or marked impairment of renal function, whether or not undergoing hemodialysis, had a higher risk of seizure activity when receiving maximum recommended doses than those with no impairment of renal function; therefore, maximum recommended doses should be used only where clearly indicated (see DOSAGE AND ADMINISTRATION).

Patients with creatinine clearances of ≤ 5 mL/min/1.73 m^2 should not receive PRIMAXIN unless hemodialysis is instituted within 48 hours.

For patients on hemodialysis, PRIMAXIN is recommended only when the benefit outweighs the potential risk of seizures.

Close adherence to the recommended dosage and dosage schedules is urged, especially in patients with known factors that predispose to convulsive activity. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of PRIMAXIN re-examined to determine whether it should be decreased or the antibiotic discontinued.

As with other antibiotics, prolonged use of PRIMAXIN may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken. While PRIMAXIN possesses the characteristic low toxicity of the beta-lactam group of antibiotics, periodic assessment of organ system function during prolonged therapy is advisable.

Drug Interactions – Since concomitant administration of PRIMAXIN and probenecid results in only minimal increases in plasma levels of imipenem and plasma half-life, it is not recommended that probenecid be given with PRIMAXIN.

PRIMAXIN should not be mixed with or physically added to other antibiotics. However, PRIMAXIN may be administered concomitantly with other antibiotics, such as aminoglycosides.

Carcinogenesis, Mutagenesis, Impairment of Fertility – Gene toxicity studies were performed in a variety of bacterial and mammalian tests *in vivo* and *in vitro*. The tests were: V79 mammalian cell mutation assay (PRIMAXIN alone and imipenem alone), Ames test (cilastatin sodium alone), unscheduled DNA synthesis assay (PRIMAXIN), and *in vivo* mouse cytogenicity test (PRIMAXIN). None of these tests showed any evidence of genetic damage.

Reproduction tests in male and female rats were performed with PRIMAXIN at dosage levels up to 8 times the usual human dose. Slight decreases in live fetal body weight were restricted to the highest dosage level. No other adverse effects were observed on fertility, reproductive performance, fetal viability, growth, or postnatal development of pups. Similarly, no adverse effects on the fetus or on lactation were observed when PRIMAXIN was administered to rats late in gestation.

Pregnancy – Pregnancy Category C: Teratogenicity studies with cilastatin sodium in rabbits and rats at 10 and 33 times the usual human dose, respectively, showed no evidence of adverse effect on the fetus. No evidence of teratogenicity or adverse effect on postnatal growth or behavior was observed in rats given imipenem at dosage levels up to 30 times the usual human dose. Similarly, no evidence of adverse effect on the fetus was observed in teratology studies in rabbits with imipenem at dosage levels at the usual human dose.

Teratology studies with PRIMAXIN® (Imipenem-Cilastatin Sodium, MSD) at doses up to 11 times the usual human dose in pregnant mice and rats during the period of major organogenesis revealed no evidence of teratogenicity.

Data from preliminary studies suggest an apparent intolerance to PRIMAXIN (including emesis, inappetence, body weight loss, diarrhea, and death) at doses equivalent to the average human dose in pregnant rabbits and cynomolgus monkeys that is not seen in nonpregnant animals in these or other species. In other studies, PRIMAXIN was well tolerated in equivalent or higher doses (up to 11 times the average human dose) in pregnant rats and mice. Further studies are under way to evaluate these findings.

There are, however, no adequate and well-controlled studies in pregnant women. PRIMAXIN should be used only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers – It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when PRIMAXIN is administered to a nursing woman.

Pediatric Use – Safety and effectiveness in infants and children below 12 years of age have not yet been established.

Adverse Reactions: PRIMAXIN is generally well tolerated. Many of the 1,723 patients treated in clinical trials were severely ill and had multiple background diseases and physiological impairments, making it difficult to determine causal relationship of adverse experiences to therapy with PRIMAXIN.

Local Adverse Reactions – Local adverse clinical reactions that were reported as possibly, probably, or definitely related to therapy with PRIMAXIN were: phlebitis/thrombophlebitis (3.1%), pain at the injection site (0.7%), erythema at the injection site (0.4%), vein induration (0.2%), infused vein infection (0.1%).

Systemic Adverse Reactions – The most frequently reported systemic adverse clinical reactions that were reported as possibly, probably, or definitely related to PRIMAXIN were: nausea (2.0%), diarrhea (1.8%), vomiting (1.5%), rash (0.9%), fever (0.5%), hypotension (0.4%), seizures (0.4%) (see PRECAUTIONS), dizziness (0.3%), pruritus (0.3%), urticaria (0.2%), somnolence (0.2%).

Additional adverse systemic clinical reactions reported as possibly, probably, or definitely drug related occurring in less than 0.2% of the patients or reported since the drug was marketed are listed within each body system in order of decreasing severity: *Gastrointestinal* – pseudomembranous colitis (see WARNINGS), hemorrhagic colitis, hepatitis (rarely), gastroenteritis, abdominal pain, glossitis, tongue papillar hypertrophy, heartburn, pharyngeal pain, increased salivation; *CNS* – encephalopathy, tremor, confusion, myoclonus, paresthesia, vertigo, headache, psychic disturbances; *Special Senses* – transient hearing loss in patients with impaired hearing, tinnitus, taste perversion; *Respiratory* – chest discomfort, dyspnea, hyperventilation, thoracic spine pain; *Cardiovascular* – palpitations, tachycardia; *Skin* – toxic epidermal necrolysis (rarely), erythema multiforme, facial edema, flushing, cyanosis, hyperhidrosis, skin texture changes, candidiasis, pruritus vulvae; *Body as a Whole* – polyarthralgia, asthenia/weakness; *Renal* – acute renal failure (rarely), oliguria/anuria, polyuria. The role of PRIMAXIN in changes in renal function is difficult to assess, since factors predisposing to pre-renal azotemia or to impaired renal function usually have been present.

Adverse Laboratory Changes – Adverse laboratory changes without regard to drug relationship that were reported during clinical trials or reported since the drug was marketed were: *Hepatic* – increased SGPT, SGOT, alkaline phosphatase, bilirubin, and LDH; *Hemic* – increased eosinophils, positive Coombs test, decreased WBC and neutrophils, including agranulocytosis, increased WBC, increased platelets, decreased platelets, decreased hemoglobin and hematocrit, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils; *Electrolytes* – decreased serum sodium, increased potassium, increased chloride; *Renal* – increased BUN, creatinine; *Urinalysis* – presence of urine protein, urine red blood cells, urine white blood cells, urine casts, urine bilirubin, and urine urobilinogen.

NOTE: Due to the high antimicrobial activity of PRIMAXIN, it is recommended that the maximum total daily dosage not exceed 50 mg/kg/day or 4.0 g/day, whichever is lower.

How Supplied: PRIMAXIN is supplied as a sterile powder mixture in vials, infusion bottles, and single-dose ADD-Vantage®† vials containing imipenem anhydrous and cilastatin sodium as follows: 250 mg imipenem equivalent and 250 mg cilastatin equivalent; 500 mg imipenem equivalent and 500 mg cilastatin equivalent.

Caution: The suspension from vials is not for direct infusion.

†Registered trademark of Abbott Laboratories, Inc.
For more detailed information, consult your MSD Representative or see Prescribing Information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486 *J9PR40(409)*

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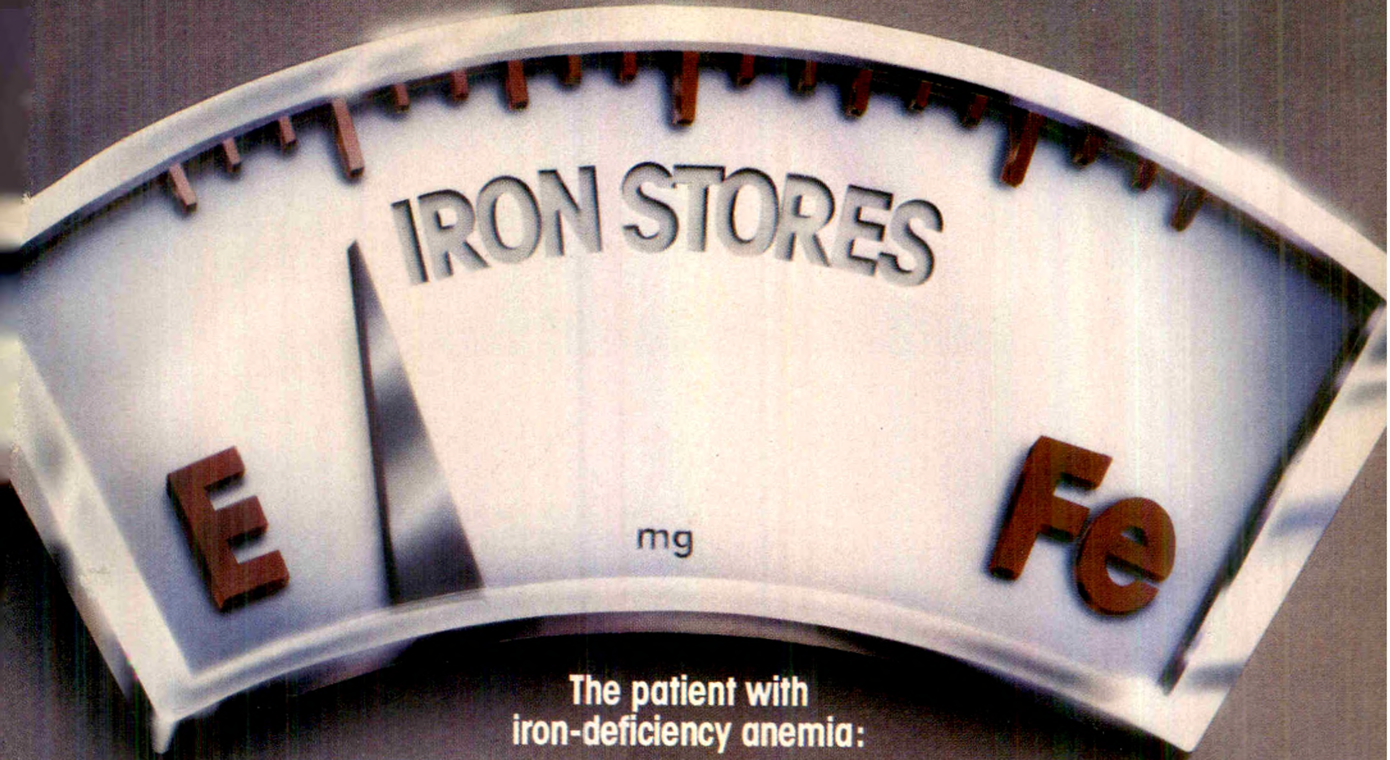

The patient with
iron-deficiency anemia:

HEADING FOR TROUBLE

Iron stores. It's imperative to replace them before they're depleted. Oral iron is the treatment of first choice. But when it fails or is impractical, another form is necessary. Fortunately, there's IMFERON – the only pharmacologic alternative to oral iron.

IMFERON restores iron reserves and rapidly restores hemoglobin within 8 days.[1] IMFERON. Efficient parenteral therapy backed by over 35 years of clinical experience worldwide.

Imferon®
Iron Dextran Injection, USP
IV/IM

AFTER GAUGING THE NEED FOR IRON

Consult boxed WARNING section of Brief Summary of prescribing information before initiating therapy.

See following page for Brief Summary of prescribing information.

AFTER GAUGING
THE NEED FOR IRON

Imferon®
Iron Dextran Injection, USP

IV
IM

CAUTION: Federal law prohibits dispensing without prescription.

WARNING:

THE PARENTERAL USE OF COMPLEXES OF IRON AND CARBOHYDRATES HAS RESULTED IN ANAPHYLACTIC-TYPE REACTIONS. DEATHS ASSOCIATED WITH SUCH ADMINISTRATION HAVE BEEN REPORTED. THEREFORE, IMFERON SHOULD BE USED ONLY IN THOSE PATIENTS IN WHOM THE INDICATIONS HAVE BEEN CLEARLY ESTABLISHED AND LABORATORY INVESTIGATIONS CONFIRM AN IRON DEFICIENT STATE NOT AMENABLE TO ORAL IRON THERAPY.

DESCRIPTION: IMFERON (iron dextran injection, USP) is a dark brown, slightly viscous sterile liquid complex of ferric oxyhydroxide and low molecular weight dextran derivative in approximately 0.9% w/v sodium chloride for intravenous or intramuscular use. It contains the equivalent of 50 mg elemental iron (as an iron dextran complex) per mL. The pH of the solution is between 5.2 and 6.5. The multiple dose vial also contains 0.5% w/v phenol (for intramuscular use only).

INDICATIONS: Intravenous or intramuscular injections of iron dextran are indicated for treatment of patients with documented iron deficiency in whom oral administration is unsatisfactory or impossible.

CONTRAINDICATIONS: Hypersensitivity to the product. All anemias not associated with iron deficiency.

WARNINGS: See Boxed WARNING.
A risk of carcinogenesis may attend the intramuscular injection of iron-carbohydrate complexes. Such complexes have been found under experimental conditions to produce sarcoma when large doses or small doses injected repeatedly at the same site were given to rats, mice, and rabbits, and possibly in hamsters.

The long latent period between the injection of a potential carcinogen and the appearance of a tumor makes it impossible to measure accurately the risk in man. There have, however, been several reports in the literature describing tumors at the injection site in humans who had previously received intramuscular injections of iron-carbohydrate complexes.

Large intravenous doses, such as used with total dose infusions (TDI), have been associated with an increased incidence of adverse effects. The adverse effects frequently are delayed (1-2 days) reactions typified by one or more of the following symptoms: arthralgia, backache, chills, dizziness, moderate to high fever, headache, malaise, myalgia, nausea, and vomiting. The onset is usually 24-48 hours after administration and symptoms generally subside within 3-4 days (such symptoms have been well recognized since iron dextran was first used). These symptoms have also been reported following intramuscular injection and usually subside within 3-7 days. The etiology of these reactions is not known. The potential for a delayed reaction must be considered when estimating the risk/benefit of treatment.

The maximum intravenous daily dose should not exceed 2 mL undiluted iron dextran.

This preparation should be used with extreme care in patients with serious impairment of liver function.

It should not be used during the acute phase of infectious kidney disease.

Patients with rheumatoid arthritis may have an acute exacerbation of joint pain and swelling following the intravenous administration of IMFERON.

PRECAUTIONS: *General:* Unwarranted therapy with parenteral iron will cause excess storage of iron with the consequent possibility of exogenous hemosiderosis. Such iron overload is particularly apt to occur in patients with hemoglobinopathies and other refractory anemias that might be erroneously diagnosed as iron deficiency anemias.

IMFERON should be used with caution in individuals with histories of significant allergies and/or asthma.

Epinephrine should be immediately available in the event of acute hypersensitivity reactions. (Usual adult dose: 0.5 mL of a 1:1000 solution, by subcutaneous or intramuscular injection.) Note: Patients using beta-blocking agents may not respond adequately to epinephrine. Isoproterenol or similar beta-agonist agents may be required in these patients.

Reports in the literature from countries outside the United States (in particular, New Zealand) have suggested that the use of intramuscular iron dextran in neonates has been associated with an increased incidence of gram-negative sepsis, primarily due to *E. coli.* This effect from the use of IMFERON in the United States has not been reported.

Information for Patients: Patients should be advised of the potential adverse reactions associated with the use of IMFERON.

Drug/Laboratory Test Interactions: Large doses of iron dextran (5 mL or more) have been reported to give a brown color to serum from a blood sample drawn 4 hours after administration.

The drug may cause falsely elevated values of serum bilirubin and falsely decreased values of serum calcium.

Serum iron determinations by colorimetric assays may not be meaningful for 3 weeks following the administration of iron dextran, particularly after large intravenous doses.

Serum ferritin peaks approximately 7 to 9 days after an intravenous dose of IMFERON and slowly returns to normal after about 3 weeks.

Examination of the bone marrow for iron stores may not be meaningful for prolonged periods following iron dextran therapy because residual iron dextran may remain in the reticuloendothelial cells.

Prolongation of the partial thromboplastin time has been reported to occur after intravenous administration of iron dextran when the blood sample for the test is mixed with anticoagulant citrate dextrose solution, USP. This interference apparently does not occur when anticoagulant sodium citrate solution, USP is used. Blood-typing and cross-matching are not affected by iron dextran.

Bone scans involving 99mTc-diphosphonate have been reported to show a dense, crescentic area of activity in the buttocks, following the contour of the iliac crest, 1 to 6 days after intramuscular injections of IMFERON.

Bone scans with 99mTc-labeled bone seeking agents, in the presence of high serum ferritin levels or following iron dextran infusions, have been reported to show reduction of bony uptake, marked renal activity, and excessive blood pool and soft tissue accumulation.

Caution should be used in interpreting results of serum iron measurements when blood samples are obtained within 1 or 2 weeks of administration of large doses of IMFERON.

Carcinogenesis, Mutagenesis, Impairment of Fertility: See WARNINGS.

Pregnancy: Pregnancy Category C. IMFERON has been shown to be teratogenic and embryocidal in mice, rats, rabbits, dogs, and monkeys when given in doses of about 3* times the maximum human dose. No consistent adverse fetal effects were observed in mice, rats, rabbits, dogs and monkeys at doses of 50 mg iron/kg or less. Fetal and maternal toxicity has been reported in monkeys at a total intravenous dose of 90 mg iron/kg over a 14 day period. Similar effects were observed in mice and rats on administration of a single dose of 125 mg iron/kg. Fetal abnormalities in rats and dogs were observed at doses of 250 mg iron/kg and higher. The animals used in these tests were not iron deficient. There are no adequate and well-controlled studies in pregnant women. IMFERON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Placental Transfer: Various animal studies and studies in pregnant humans have demonstrated inconclusive results with respect to the placental transfer of iron dextran as iron dextran. It appears that some iron does reach the fetus, but the form in which it crosses the placenta is not clear.

Nursing Mothers: Caution should be exercised when IMFERON is administered to a nursing woman. Only traces of unmetabolized iron dextran are excreted in human milk.

Pediatric Usage: Not recommended for use in infants under 4 months of age (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: *Severe/fatal:* Anaphylactic reactions have been reported with the use of IMFERON; on rare occasions these reactions have been fatal. Such reactions, which occur most often within the first several minutes of administration, have been generally characterized by sudden onset of respiratory difficulty and/or cardiovascular collapse. The incidence of these acute hypersensitivity reactions has been estimated between 0.2% to 0.3%. (See boxed WARNING and PRECAUTIONS: *General,* pertaining to immediate availability of epinephrine.)

Mild/moderate: Delayed reactions (see WARNINGS). The incidence of delayed reactions reported in a longitudinal study of patients given multiple intravenous injections of IMFERON, usually 5 mL or greater, was approximately 8% (4% of the total number of injections given).

Other systemic/local: Isolated or multiple signs/symptoms with varying severity have been reported.

Cardiovascular: Chest pain, shock, hypotension, tachycardia, flushing. (Flushing and hypotension may occur from too rapid injections by the I.V. route.)
Dermatologic: Urticaria, pruritus, purpura, rash.
Gastrointestinal: Abdominal pain, nausea, vomiting, diarrhea.
Hematologic/lymphatic: Leucocytosis, lymphadenopathy (generally inguinal and associated with I.M. injections).

Musculoskeletal/soft tissue: Arthralgia, arthritis (may represent reactivation in patients with quiescent rheumatoid arthritis—see PRECAUTIONS: *General*), myalgia, including backache; abscess formation (sterile); necrosis; atrophy/fibrosis (I.M. injection site); cellulitis, swelling; brown skin and/or underlying tissue discoloration (staining) (See CLINICAL PHARMACOLOGY), soreness or pain at or near intramuscular injection sites, which in some isolated instances was reported to persist for over a year; variable degree of inflammation; local phlebitis at or near I.V. injection site.

Neurologic: Convulsions (may accompany anaphylaxis), syncope, headache, weakness, paresthesia, febrile episodes, chills.
Respiratory: Bronchospasm, dyspnea.
Urologic: Hematuria.
Miscellaneous: Febrile episodes, sweating, chills.

OVERDOSAGE: Overdosage with IMFERON is unlikely to be associated with any acute manifestations. Excessive doses of IMFERON beyond the requirements for restoration of hemoglobin and replenishment of iron stores, may lead to hemosiderosis. Periodic monitoring of serum ferritin levels may be helpful in recognizing a deleterious progressive accumulation of iron resulting from impaired uptake of iron from the reticuloendothelial system in concurrent medical conditions such as chronic renal failure, Hodgkins disease, and rheumatoid arthritis. The LD_{50} of IMFERON is not less than 500 mg/kg in the mouse.

Dialysis: A study of [59Fe] iron dextran utilizing isotonic saline in a 4-hour *in vitro* dialysis run, indicated that less than 0.5% of the injected radiolabeled iron dextran traversed the dialysis membrane.

HOW SUPPLIED: *For intramuscular or intravenous use:* 2 mL ampules, boxes of 10: NDC 0585-2226-10

For intramuscular use ONLY: 10 mL multiple dose vial containing 0.5% phenol as a preservative, boxes of 2: NDC 0585-3226-20

CAUTION: Federal law prohibits dispensing without prescription.

Store at room temperature, preferably below 86°F. Do not freeze. Keep out of the reach of children.

See package insert for Full Prescribing Information.

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* The human dose presented here is the total iron required for treating an iron deficient state in a representative patient. The calculation represents a 50 kg patient with a hemoglobin value of 8 g/dL requiring 30 mL of IMFERON or 1500 mg iron—equivalent to 30 mg/kg.

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ROCHESTER, NY 14623 U.S.A.

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Reference: 1. Mangana L, Dhar SK, Smith FC, et al: Iron absorption and utilization in maintenance hemodialysis patients: Oral and intravenous routes. *Mt Sinai J Med* 1984;51:180-183.

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New England Surgical Society

This issue of the *Archives of Surgery* records the 1989 scientific proceedings of the New England Surgical Society (NESS). Regional societies are part scientific, part social, part reunion, even political. Driving to the NESS meeting through Connecticut and New Hampshire on Route 91 to the historic Mount Washington Hotel in Bretton Woods, NH, provided an opportunity to view the beauty of New England in late September. The changing fall colors, the running creeks and rivers, the majestic blue spruce, and the quietude of the countryside were vintage Mother Nature. One could not resist reminiscing about the symbolic significance of New England to Americans, where multiple historic sites are surrounded by distinguished institutions of higher learning. The snow-capped Washington mountains served as a backdrop for this meeting where the fresh air was invigorating for an urban dweller. The Editor, as an invited guest, easily assimilated the mood of the NESS meeting.

Mount Washington Hotel reminds a Westerner of the famed Del Coronado of San Diego with its relaxed atmosphere, high ceilings, rambling circular porches, tennis courts, heated swimming pool, and golf course. During the NESS meeting, this hotel offered the guests good service and excellent food, which was combined with rain, snow, cold weather, and a prolonged power loss that disrupted modern conveniences and slightly altered the timing of the meeting. This was balanced by the presence of and warm exchange between some of New England's best surgeons. Their conversations and gatherings in the hotel lobby and on the wide porches of the hotel were animated with recollections from medical school, surgical residencies, professional challenges, and family friendships. These animated conversations covered recently acquired professorships, academic musical chairs, the latest update on their children, available academic positions, grantsmanship trends, "Whose neck is on the block?", shortcomings of this year's NESS program (translated to mean their paper was not accepted), deans needing careful grooming, the Harvard Relative Value Schedule, and, surprisingly, that no major surgical journal editors are based in New England. The old circular dining room reminds one of The Homestead, site of many American and Southern Surgical Association meetings. Here, reminiscences of their undergraduate and medical school experiences at Harvard, Yale, Groton, and the MGH, and the good old days of better NIH funding permeated the discussions.

Part of the lagniappe of American surgery is membership in and attendance at regional surgical society meetings. The NESS annual meetings date back to 1917 when Samuel Mixter served as its first president. Many of our colleagues prefer regional meetings over national meetings. They are usually conducted at a more leisurely pace, are more intimate, allow time for camaraderie, and provide better access to and exchange with speakers.

The 1989 presidential address, the highlight of this meeting, lived up to member expectations. President James Foster, professor and former chairman of the Department of Surgery at the University of Connecticut, spoke on "Some Eastern Thoughts for Northeastern Surgeons." It was an impressive, impeccably documented, value-oriented, superbly delivered speech with significant philosophical depth. This address will be quoted often in future years. The selection of this pioneer in liver surgery as NESS President was a wise and popular choice. Close friends usually ponder about the "spouse factor" in preparing and editing presidential addresses!

The traditional "In Memoriam" to those members deceased since the 1988 meeting listed well-known American surgeons: Richard Wilson, George Clowes, David Boyd, and Charles Mixter, Jr. These moments of silence are reflective and sobering. The papers mirrored the variety of clinical and research topics common to surgeons throughout the country. Discussions were spirited, occasionally entertaining, but mostly penetrating and inquisitive. The business meeting, as expected, was short, well moderated, with organized committee reports, a membership election process, and a well-received audit report (books balanced . . . no dues increase).

A rare privilege for the Editor was the response of the recipient of the Nathan Smith Distinguished Service Award from the NESS, the venerable Francis Moore, professor emeritus at the Harvard Medical School and former surgeon-in-chief at the Peter Bent Brigham Hospital. Moore, in an eloquent acceptance, continued to defy the odds by avoiding dangling participles, split infinitives, and nonparallel sentence structure. The only previous award recipient, Claude Welch of Boston, lent his dignified presence to the occasion.

The Fifth Annual Jason Mixter Lecture by Alexander J. Walt, professor and former chairman of the Department of Surgery at Wayne University School of Medicine, on "The Impact of Technology in the Management of Pancreatic Pseudocysts: 1970-1989," was delivered in vintage Walt style, with clarity, facts, and new ideas—all of which demonstrated great respect for the pancreas. The message and the messenger were excellent.

The President's banquet carried a thoughtful touch: Doris Armstrong, a nurse with a distinguished operating room career and active in nursing circles, was the banquet speaker. Using pictures and poetry, Armstrong reminisced about surgeons with whom she had worked for 25 years. The respect and interdependence of these professions was never more apparent and pleasing.

As NESS members took leave of their 1989 meeting, the planning process for 1990 immediately began. A new presidential address is initiated, the program committee is activated, membership applications are completed, social activities are planned, and a meeting date is reserved on the calendar. Such is the nature of regional surgical society meetings. They represent a scientific forum for residents and junior faculty and early peer review as a stepping stone to national organizations. The vitality of regional surgical societies continues to be an important segment of the American surgical education process.

Claude H. Organ, Jr, MD
Editor

Commentary

The Surgeon and Colorectal Cancer Genetics

Case Identification, Surveillance, and Management Strategies

Research in the causes of colorectal cancer (CRC) has accelerated at an explosive rate during the past two decades.[1] Much has changed since Sklifasowski[2] first noted the connection between polyps and CRC. Its genetic implications subsequently led to the characterization of familial adenomatous polyposis (FAP), which is unquestionably the best known example of hereditary (autosomal-dominant) CRC. Familial adenomatous polyposis has been a great teacher. It had been considered for many decades to be a very simplistic disease, with its phenotype (colonic polyps and cancer) restricted to the colon. However, in the early 1950s, Gardner and Richards[3] significantly changed this concept when they described extracolonic signs, namely, cutaneous (epidermoid cysts) and osseous (osteomas), in a large kindred prone to colonic polyps and CRC. This variant is now known as Gardner's syndrome. Nakamura et al[4] subsequently showed that Gardner's syndrome was linked to the FAP locus on the long arm of chromosome 5.

The tumor spectrum in FAP, inclusive of its phenotypic variant Gardner's syndrome, has shown a remarkable increase during the past couple of decades. Periampullary carcinoma is the most common cancer following CRC. Cancers of the stomach (particularly among the Japanese), small bowel, pancreas, thyroid, adrenal cortex, sarcomas, and brain tumors have been demonstrated as integral lesions in FAP. Desmoids (particularly intra-abdominal) are a further ominous problem in certain FAP kindreds.[5] The recognition of these diverse tumor sites has been presumed to be due, in part, to the intensity of the search for cancers of *all* anatomic sites and to increasing longevity because of prophylactic colectomy. While FAP accounts for less than 1% of the total CRC burden, it nevertheless remains a prototype for hereditary cancer predisposition and for cancer control. Knowledge of its natural history, particularly the early occurrence of adenomatous polyps—beginning almost invariably in the rectal sigmoid area and being the ultimate CRC occurrence—mandates prophylactic colectomy when the phenotype is discerned. Endoscopy is the screening procedure of choice, and it is important to maintain surveillance of these patients for the rest of their lives, given their inordinate susceptibility to cancers of diverse sites (Table).

FAMILIAL COLON CANCER (FCC)

Familial colon cancer is arbitrarily characterized by the presence of two or more first- and/or second-degree relatives with CRC in the absence of florid colonic polyps. Age at onset, anatomic site, and incidence of synchronous/metachronous colonic cancer occurrence corresponds to expectations from the general population. There is no excess of extracolonic cancer sites. A first-degree relative of a patient with FCC has a risk for colon cancer that is two to three times higher than that for individuals in the population who lack a first-degree relative with colon cancer.[1] It should not be surprising that FCC is common, given the increased frequency of colon cancer in most western civilizations. The causes of FCC are believed to be multifactorial, meaning that there is interaction between host and environmental factors. Many occurrences may be due to chance alone. An unknown fraction may be hereditary, resulting from a spontaneous germinal mutation in one of the parental germ cell lines. These high-risk patients merit increased surveillance (Table).

DISCRETE COLONIC POLYPS AND COMMON CRC

Discrete colonic polyps and common CRC may also have a hereditary cause.[6] This association has recently been described in a series of families wherein the frequency of the deleterious gene for occasional colonic polyps and CRC susceptibility was found to be about 20%, with penetrance of 60% by age 60 years.[7] As in FCC, the natural history of CRC in this condition is comparable with that for CRC in the general population, factors that are important for cancer control strategies (Table).

The distinction between FCC and discrete colonic polyps and common CRC may be blurred, or, conceivably, they may be one and the same phenomenon. Undoubtedly, an unknown fraction of these patients, following intensive medical genetic study, may be found to manifest hereditary nonpolyposis colorectal cancer (HNPCC), which is discussed in the following section.

HNPCC

Recognition of what is now classified as HNPCC dates to Warthin's[8] original observations on family G, initiated in 1895 and published in 1913. In the mid-1960s, Lynch and Krush[9] updated the observations on family G when they were provided all of Warthin's original pedigrees and records. This offering followed the description of an autosomal dominantly inherited syndrome of colon cancer in the *absence* of multiple polyps in two extended kindreds.[10] Since that time, Lynch and colleagues have continued to provide further detailed definition of the syndrome's natural history, including an expansion

Classification, Surveillance, and Management Strategies*

Recommendations	FCC	Hereditary Discrete Common Polyps and CC	FAP	HNPCC
Age for initiation of patient education	30-35 y	30-35 y	Preteens	Teens
Age for fecal occult blood test	30-35 y, and then semiannually	30-35 y, and then semiannually	Would not perform, given endoscopic surveillance	Would not perform, given endoscopic surveillance
Endoscopy†	35 y of age and every 2 y thereafter	35 y of age and every 2 y thereafter‡	10 y of age and once a year thereafter; indirect ophthalmoscopy for CHRPE	Full colonoscopy at 25 y of age and every 2 y thereafter through 35 y of age, and then annually
Surgery	Same as for general population indications	Same as for general population indications	Prophylactic subtotal colectomy vs total colectomy with pouch and reconstruction	Subtotal colectomy
Extracolonic organs requiring special cancer surveillance	None	None	Periampullary, stomach (particularly in Japanese), small bowel, pancreas, sarcoma, thyroid, brain tumors; desmoids	Endometrium, ovary, urologic (kidney, ureter, bladder), small bowel, bile duct, stomach, breast

*FCC indicates familial colon cancer; CC, colon cancer; FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colorectal cancer; and CHRPE, congenital hypertrophy of the retinal pigment epithelium.

†Endoscopy should be repeated every 6 months or every year if polyps or other abnormalities are present.

‡Prophylactic colectomy should be considered if there are 5 to 10 or more adenomatous polyps present and/or if there is recurrence of polyps.

of cancer susceptibility sites. Screening/management strategies for HNPCC have also been developed[1] (Table).

Hereditary nonpolyposis colorectal cancer is currently described as including two variant forms: Lynch syndrome I, with an autosomal dominantly inherited susceptibility to early-onset CRC in the absence of diffuse polyposis, predominance of cancer *proximal* to the splenic flexure, and an excess of synchronous and metachronous colonic cancers; and Lynch syndrome II, which shows all of the features in Lynch syndrome I, but also shows an excess of integrally related cancer types that have been described over the years in Lynch syndrome kindreds.[1] The association of endometrial carcinoma with HNPCC was clearly defined in the early studies by Lynch et al.[10] More recently, studies of Lynch syndrome II kindreds have provided more extensive information on the spectrum of cancers of differing anatomic sites. These have included gastric cancer,[11] carcinoma of the larynx,[12] carcinoma of the urological system (particularly transitional cell carcinoma of the ureter and carcinoma of the kidney),[13] carcinoma of the ovary,[14] carcinoma of the pancreas,[15] adenocarcinoma of the small bowel,[16] and small-bowel cancers and B-cell lymphatic leukemia.[17] The full tumor spectrum of HNPCC remains enigmatic but is being expanded as new evidence accrues.

The mounting evidence for cancer of diverse anatomic sites in HNPCC raises important questions regarding the underlying genetic origins and clinical classification. More important are the implications for developing additional surveillance/management strategies for these cancer sites when found to be integral in certain HNPCC kindreds (Table).

Hereditary nonpolyposis colorectal cancer poses difficulty in its diagnosis due to the lack of premonitory clinical signs and/or biomarkers of cancer genetic susceptibility. Thus, the family history must remain the key to its recognition.

In many circumstances, a detailed family history may not be possible. However, identification of certain components of HNPCC in the nuclear family may provide clues for a tentative diagnosis of HNPCC. This information should be sufficient for surgical judgment, particularly with respect to performing a subtotal colectomy vs a more limited resection in a given patient. It may be equally valuable for initiation of surveillance for that patient's primary relatives. The following are clinical examples where "limited" family history may enable a presumptive HNPCC diagnosis.

Nuclear Family 1

Two brothers at ages 36 and 39 years manifested proximal colon cancer in the absence of multiple colonic polyps. Each underwent a hemicolectomy. Each subsequently developed metachronous colonic cancer. Their mother had had endometrial carcinoma at age 45 years. This family history is significant. The progeny of the two colon cancer–affected brothers merit intensive surveillance (Table). Other potentially at-risk relatives must be identified.

Nuclear Family 2

A 25-year-old man manifested carcinoma of the ascending colon in the absence of multiple colonic polyps. His mother had manifested endometrial carcinoma at age 35 years and proximal colonic cancer at age 42 years. This history was sufficiently compelling to perform a subtotal colectomy on this 25-year-old man.

Nuclear Family 3

We are currently following up a family in which two brothers at ages 22 and 29 years manifested proximal colon cancer in the absence of multiple colonic polyps. Their father is 55 and their mother is 52 years of age, and each is cancer-free. The mother's family history was unremarkable. The father had a brother with colon cancer at age 38 years, although the anatomic site in the colon was unknown. This individual had a daughter with proximal colonic cancer at age 30 years. The father is most likely an obligate gene carrier. He may eventually develop cancer or, due to reduced gene penetrance, may remain cancer-free. On the strength of these findings, we have recommended that all primary relatives of these cancer-affected individuals be under intensive cancer surveillance (Table). Should any develop colonic cancer, then the surgical procedure of choice would be subtotal colectomy. Women in this high-risk category who develop colonic cancer and who have completed their families should be considered as candidates for prophylactic hysterectomy and bilateral salpingo-oophorectomy (Table).

Nuclear Family 4

A 32-year-old man manifested carcinoma of the cecum in the absence of diffuse polyposis. There was no evidence of CRC or gynecologic cancer in his paternal and maternal lineages. Three years after hemicolectomy, he developed metachronous CRC. A subtotal colectomy was recommended, given the assumption that the patient represented a germline HNPCC mutation. His progeny will be candidates for our intensive surveillance/management strategies (Table). In retrospect, this patient may have been a candidate for subtotal colectomy as opposed to hemicolectomy at the time of his initial cecal carcinoma. We suggest that all patients presenting with proximal CRC onset at less than age 40 years, in the absence of diffuse colonic polyps and even in the presence of a *negative* family history of CRC, be considered for subtotal colectomy. Patients of this type epitomize the priority need for development of biomarkers that correlate with the deleterious HNPCC genotype.

These anecdotal case reports are the type of presentations of HNPCC that will be encountered frequently in the typical surgical practice setting. Many other variations in these cancer phenotypic presentations within nuclear families will be equally compelling for presumptive HNPCC diagnosis. Given the variation in age at onset and anatomic site of colonic cancer that may occur in HNPCC kindreds, I consider this diagnosis to be present when encountering any family with three or more primary relatives who manifest CRC wherein at least one had age of onset at less than 40 years, and where diffuse colonic polyposis could be excluded. Confidence in HNPCC diagnosis will be increased in direct proportion to the frequency of occurrences of earlier age of onset, proximal location, and an excess of synchronous/metachronous colonic cancer. Endometrial or ovarian cancer, or other cancers integral to HNPCC, among first-degree relatives will also be of genetic diagnostic significance. Until a biomarker with acceptable sensitivity and specificity to the HNPCC genotype is discovered, these more crude measures of HNPCC diagnosis must continue to be pursued. Some of these issues are expressed in probability terms in the following section.

PROBABILITIES OF EARLY-ONSET COLON AND ENDOMETRIAL CANCER

To appreciate the probability of manifesting early-onset colon and/or endometrial carcinoma prior to age 40 years, their likelihoods have been compiled based on age-specific colon and endometrial cancer incidence from the Surveillance, Epidemiology, and End Results program data. These studies indicate that the probability of manifesting colon cancer by age 40 years is 7×10^{-4}, and of endometrial carcinoma by age 40 years is 4.4×10^{-4}. The probability of a woman's having both colon and endometrial cancer onset prior to age 40 years, if these diseases are unrelated, is 0.00044×0.0007, or 3 in 10 million. This same probabilistic approach was given to the assessment of proximal colon cancer, which occurs in about 35% of all patients with colonic cancer. Herein, the probability of proximal colon cancer in a patient less than age 40 years would be 0.35×0.0007, or 2.5×10^{-4}. Therefore, assessing the clinical significance for early-onset colorectal and endometrial cancer, including their combination in a single patient, provides an appreciation for their chance expectations in the general population.

BIOMARKER RESEARCH AND CRC

Recently, two groups[18,19] identified restriction fragment length polymorphism markers on the long arm of chromosome 5 that were tightly linked to the gene for FAP. In addition, sporadic colorectal carcinomas showed loss of heterozygosity on the long arm of chromosome 5 in 20% to 30% of cases.[20-22] This suggests that the FAP gene on chromosome 5 is involved in the origins of hereditary and sporadic CRCs.

The molecular genetics of the HNPCC syndromes have been difficult to characterize because of the lack of a premonitory biomolecular marker or phenotypic manifestation for this disease.[23] The gene for Lynch syndrome II has been provisionally linked to the Jk (Kidd) blood group on chromosome 18.[24,25] Sporadic colorectal carcinomas show chromosome 18 deletions. This may represent the *loss* of a tumor suppressor gene, and a candidate gene has been recently identified by Vogelstein et al.[26] The Lynch syndrome II gene may be located on chromosome 18, and this may be the same gene involved in the causes of sporadic CRC.

Two other types of genetic alterations that have been reported in colorectal tumors include (1) point mutations in *ras* proto-oncogenes[27,28] and (2) allelic deletion of chromosome 17.[26,29,30] Recent studies have also shown that the 53p gene on chromosome 17p is mutated in CRCs, suggesting that 53p inactivation accounts for the observed chromosome 17 deletion.

Vogelstein et al[26] found that these four molecular alterations accumulated in a fashion that paralleled the clinical progression of tumors. For example, allelic deletions of chromosome 5 and *ras* mutations occurred relatively commonly in early-stage adenomas as well as later-stage tumors. In contrast, allelic deletions of chromosomes 17 and 18 occurred only occasionally in earlier-stage carcinomas, but occurred frequently in advanced adenomas and in carcinomas. Clinical and pathological associations also showed that allelic deletions of chromosomes 17 and 18 identified a subset of patients with CRC with increased predilection for distant metastases and cancer-related death.[31]

The development of CRC in sporadic and hereditary cases appears to result from the accumulation of several specific genetic changes.[32] For example, Law et al[30] reported allelic loss in patients with Lynch syndrome on chromosomes 5 and 18, and Boman et al[32] described allelic loss in patients with FAP on chromosome 18. As in the case of FAP, it is tempting to speculate that germinal mutations occurring in HNPCC may involve the same or similar genes that are affected somatically in sporadic CRCs in the general population. The finding of the HNPCC gene(s) location will have potentially greater significance than even the discovery of the "polyposis gene." This is because of the greater frequency of HNPCC and the association with carcinomas at extracolonic sites. Moreover, such a preclinical marker is more essential to the design of clinical screening programs, given the lack of pre-of-the-art laboratory equipment and personnel to conduct formal investigations in the interest of furtherance in our knowledge base.

Computerized programs would enable assembly of an extended kindred so that identification of risk status on its membership would be possible. This would enable primary physicians caring for these patients to be provided with a computerized readout on their specific patient, giving the patient's colonic cancer risk, characteristics about the natural history of cancer expression in the particular hereditary form (FAP or HNPCC), and the most current surveillance and management recommendations. When biomarkers become available, they can be immediately entered into this computer readout.

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In Other AMA Journals

ARCHIVES OF INTERNAL MEDICINE

Methotrexate-Induced Cirrhosis Requiring Liver Transplantation in Three Patients With Psoriasis: A Word of Caution in Light of the Expanding Use of This 'Steroid-Sparing' Agent

Stanley C. Gilbert, MD; Göran Klintmalm, MD, PhD; Alan Menter, MD; Alan Silverman, MD

Methotrexate has been used for many years to treat refractory psoriasis. Three cases of methotrexate-induced cirrhosis requiring orthotopic liver transplantation are presented to emphasize the importance of strict adherence to published criteria for patient selection, monitoring of cumulative drug dosages, and the performance of serial liver biopsies. Each patient had been treated with long-term methotrexate therapy (cumulative doses far in excess of 1.5 g) without undergoing serial liver biopsies, contrary to well-established treatment guidelines. Caution must be exercised in using methotrexate as a steroid-sparing agent in the treatment of inflammatory diseases because of its potential to cause severe hepatotoxic effects with long-term usage and cumulative doses above 1.5 g. Patients easily become psychologically dependent on the drug, and physicians need to guard against the false sense of security engendered by normal results on liver function studies (*Arch Intern Med.* 1990;150:889-891).

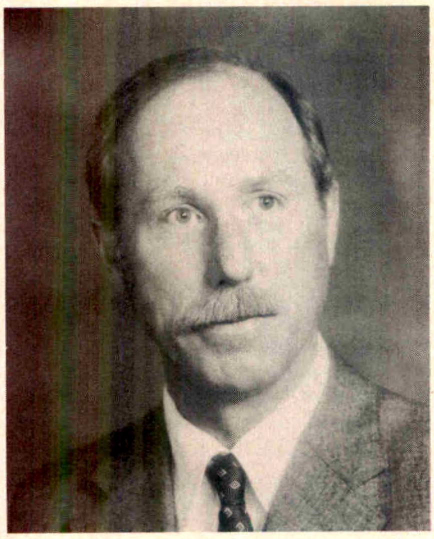
Reprint requests to Baylor Psoriasis Center, 3600 Gaston Ave, Wadley Tower, Dallas, TX 75246 (Dr Menter).

Papers Read Before the 70th Annual Meeting of the New England Surgical Society, Bretton Woods, NH, September 22 to September 24, 1989

Some Eastern Thoughts for Northeastern Surgeons

Presidential Address

James H. Foster, MD


James H. Foster, MD

Progress might have been all right once, but it has gone on far too long.

OGDEN NASH

A doctor who prescribes an identical treatment for an identical disease in two individuals and expects an identical development may be properly classified as a social menace.

LIN YUTANG

I have watched with fascination the emerging dominance of the Eastern nations in the political and economic spheres, and I agree with the majority opinion that we must credit hard work, good schooling, and a greater concern for society than for the individual for much of their competitive edge. However, it is not of capitalism vs socialism that I wish to speak today, but rather of certain cultural values that distinguish West from East, values that may have some pertinence to the way we practice medicine.

I have no valid credentials for talking about Eastern values. I have spent a total of slightly less than 4 months on four different trips to the Orient, and much of that time was in the countryside. However, I have read and thought a bit in the 2 years that you give your president elect to choose and to mature a topic. The Eastern theme seemed an appropriate vehicle with which to expose some of my biases. I have leaned more heavily on the contributions of India and China, on Hindu and Buddhist teachings and the secular wisdom of Confucius, Laotse, and others than I have on Japan. It seems to me that in many ways the warrior tendencies of the Japanese and their rapid development of industrial and commercial strengths puts them in the Western camp. I plan to introduce an idea and then to relate it to our own practice, and thus to discuss such matters as humility, ambivalence, patience, science, courtesy, and even death.

The Eastern artist often simplifies, not in the sense of making easy or even clarifying, but in concentrating on essentials. “Reduce” is the verb often used for this process, but the result is often to elevate the message. The poet does this well. A sonnet has only 14 lines, Haiku but 17 syllables. “Keep your eye on the ball” is the Western translation of this principle, but that is advice we often forget in our practice of medicine. On the contrary, our excessive dependence on the lesser gods of Technology and Chi-square Analysis has brought medicine to a complexity that hovers on the brink of absurdity. The experienced clinician can still separate the wheat from the chaff with a minimum of testing, but that cannot be said any more of the modern trainee. Perhaps the economic constraints being imposed on us will have a good side. We may even be forced to reduce expense by going back to doing

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[redacted]

less than five, lymph nodes involved and positive hormone receptors? Maybe not, but you can be sure that some acronymonious group has shown, in a properly controlled, prospective, double-blind, randomly selected trial that a white *left-hander* needs something else. I do not even bother any more to learn the latest "scientific truths" about the treatment of breast carcinoma, first, because my aged memory is fading and, second, because I know there will be a different recommendation in 6 months. However, it comforts me to know that statistics continue to be used creatively by physicians not yet hopelessly mired in science and mathematics. One can always find an article whose numbers will support one's current biases.

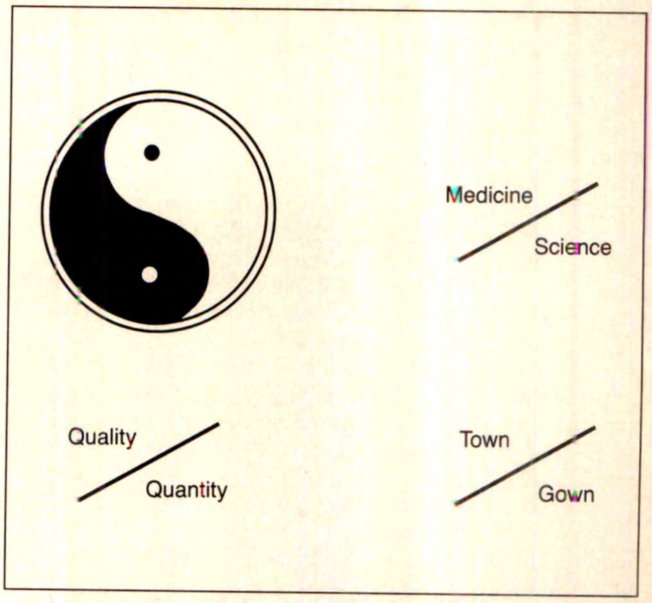
Another example of the confounding effects of mindless data collection is provided by the quality assurance process. We all want to assure quality—it's the ethical foundation of medical practice. But I speak now of a recent phenomenon, the quality assurance process mandated by regulatory bodies often more interested in economic control than in excellence.

Well-meaning but misguided people, who were probably toilet-trained at too early an age, have come to believe that you can measure the quality of patient care with a yardstick marked out in reproducible units that can be applied by clerks. A noble idea in a noble cause, but unfortunately the units that can be measured are often not the significant ones. I suppose music can be measured in vibrations per second, literature by counting words, and the merit of a scientist by counting his publications, but something is lost in the process. One can only hope that this peer review process will pass through its "anal" phase quickly and move on to something more constructive. Today we even grade residents' performances by numbers to make the process more "scientific." My suggestion would be for the enthusiast to try that at home. Surely it ought to be helpful and constructive to evaluate numerically our wives and children as well. It might be fun to observe the result.

Much of this balderdash evolves from a computer mentality that can only look at quantifiable material. As computers have become more able and available, our delight with these sophisticated toys has allowed our enthusiasm to overtake our judgment. The generation and manipulation of numbers create more publications, which then seem to grow on themselves. As our scientific journals multiply, their usefulness diminishes. Anything with data is published. I rail not against real science that is driven by ideas, by new insights intuitively arrived at and then proved by creative experiments. What I decry is the "pseudoscience" that begins with data and ends with data without any intervening thought. That's not science, that's not deductive reasoning; that's measurement.

Another Eastern concept that deserves our attention is that of yin and yang (Figure). Yin refers to female, earthly, passive, cold, and dark; yang is male, positive, and active and embodies the celestial principles of light, heat, and life. Yin is rest; Yang is motion. Today, for my own safety, I would like to ignore the sexist part of this. I want to contrast the complementary nature of these Eastern symbolic principles with the neutering effect of Western democratic compromise. No man or woman, no action, no philosophy is pure yin or yang to the Chinese humanitarian, and yet there is no mixing and dilution to dull gray perceived when these contrasting principles appear together. Instead, a creative tension is produced that adds to delight and to understanding.

Let me try to apply the concept first by contrasting medicine and science. Great credit is due those few who must know and who have the genius, the insight, and the industry to divine the rules and regulations of natural phenomena, who persist at the bench to prove their hypotheses with repeatable experiments based on objective measurements. But if you will accept my definition of medicine as "the attempt to relieve suffering caused by disease," much of what we do is not scientific—nor should we be apologetic. Reducing life to measurable aliquots is an absolutely necessary step in understanding some aspects of it, but it may be a step aside rather than a step forward in the care of an individual patient. Most important things deny the yardstick. Can we measure judgment, experience, or skill in dissecting an adhesion or comforting a family? Can we measure the joy that comes with the marriage of gin and vermouth or clouds at sunset? Should a kiss be measured in dynes of pressure per square centimeter or millions of bacteria transferred per second? When we finish chipping away at the mountain of science, will we be left with a field of rubble? When we explore to its origins every branch of the Amazon or of science, will we be too specialized, too distant from one another even to communicate? The only thing that can hold us or bind us together is our common humanity. Of course science and technology are important. Without them, there would be no chance for the 5 billion of us to exist safely on this planet, and certainly no way to feed or save from the ravages of pollution the 10 billion of tomorrow. Science and technology are the asphalt over which we travel more swiftly and more easily. They have accelerated the pace of required decision, but they can provide neither direction nor goal to thinking man.



The Chinese yin-yang concept symbolizes the harmonious interrelationship of contrasting principles.

Town/gown conflicts have their basis in a similar dichotomy. The academician gets his kicks from successful experiments, grants funded, and papers published. He looks down on the unscientific nature of most medical practice. The practitioner, in turn, derides the scientist for his ineptness at the bedside. Both parties feed this conflict with their insecurities because our Western ethic says that the medical scientist ought to be an effective doctor and that the practitioner ought to be a scientist. Why so? Why can we not realize that the dichotomy is natural, probably useful, and almost certainly inevitable? The Westerner does not deal comfortably with paradox. Ambivalence makes us nervous, doesn't it?

The quality/quantity thing provides another example. Is it not the concern for quality that sets man apart from the rest of the animal world? Our ability to set values and establish goals is our highest achievement. Quality and quantity are not natural enemies, but they are different. I am afraid that our

Western culture has hopelessly confused these two terms. What is the value of a van Gogh painting or a golfer's victory in the Masters? Most of us would answer that question today in quantitative terms, ie, in dollars. What an enormous transgression of what quality and value really mean, and we do not even notice the difference. Many Easterners have rejected Western materialistic values, even when acceptance would greatly improve their creature comforts. Their values reflect more concern with quality than with quantity, and they should make us pause. If we know what quality, what excellence is in medical care (and I think that most of us do), we should not participate in a process that measures the wrong things and judges therefrom. Go back and read Thoreau's *Civil Disobedience* before you go to your next quality assurance meeting. We should not stonewall efforts to judge quality; in fact, we must encourage them and play leadership roles. But let us do what we can to get the regulators off of their quantitative kick.

The modern Western view of society and politics is economic, legalistic, and mathematical—materialistic, if you will. Medicine is becoming increasingly misshapen in the same direction, but medicine is not, should not, must not be a profession based on economic or legal values. We forget that at our peril. Medical prices may have some vague relationship with costs but are in no way related to value. When was the last time you charged for talking with a patient's family? Yet we often spend more time talking with the family than with the patient.

We must not let the amorality of the marketplace be an excuse for dispensing with the selfless ethic that medicine has followed for millennia. It is that ethic rather than our science and technology that commands the respect of our patients and the public. That ethic and those values have no measurable price and never will.

There is more kindness, truth, humor, and sadness, more depth and richness in a doctor's office than in any corporate headquarters or government bureau, and it is kindness and truth, humor and sadness that are the real stuff of life. In this secular age, our profession can probably remind our patients and the public of our common humanity more effectively than even the clergy—*if* we remain true to our core. Our attitudes even more than our skills can make a mark in reaffirming the values that count.

Man's heart has been hardened by science, by economics, and by politics. It can be softened by kindness, courtesy, and integrity in our professional and personal lives. The Oriental is famous for his courtesy—his attempt to consider the other person's feelings more than his own. That attitude is not very popular in the United States today. In fact, courtesy and self-restraint may be taken as signs of weakness or unintended acquiescence. Indeed, their use by our profession may allow short-term political and economic setbacks, but their moral force will prevail in the long run. Confucius would regard many politicians and businessmen of today as barbarians—without ethics, without manners, with every action dictated by self-serving interests. What would he think of the surgeons of today?

I'm beating awfully hard on Western culture this morning—obviously exaggerating to make points. Moralizing is always easier on the preacher than the preachee, and I apologize for my fervor. But the fundamental difference between East and West that I would like to stress is that the Easterner believes that values and attitudes are more important than measurements and prices. Quality is more important than quantity, and principles are more important than facts and data.

Principles, however, can be very rigid masters. In the Confucian scheme of things, they must be balanced with expediency. Subtlety, negotiation, and a certain inexactness often save the day. The Oriental has little use for the strength of some Prussian, British, or even American redneck convictions. He may not even admire surgical decisiveness or what we would call "scientific" objectivity. More yin and yang here. Wisdom, humility, and patience. It bothers the exact, logical, tidy, solution-seeking Western mind, doesn't it?

Principle must also be tempered with mercy. As we try to assure quality by peer review, we must insist on the highest standards of care and absolutely honest reporting. Every resident must learn this by example, by fiat, and by nonacceptance without review of any untoward event. Unfortunate "acts of God" occur less often to the patients of surgeons who openly and frequently review their problems together. Our intolerance of sham, of dishonesty or neglect, and of incompetence must be absolute, but our discussion and decisions about maloccurrence to our own patients and those of others must be tempered by the knowledge that we are imperfect and our patients' problems are often insurmountable. The effects of medicine and the meddling we call operation are complex and to a large extent not yet understood. It is no wonder that the outcome is uncertain. We must be more critical of ourselves than of our fellows. High standards do not disallow humility on our part and generosity to others. Who was it who said that perfection is the enemy of good?

Eastern culture is also noted for its reverence—reverence for all forms of life, for quiet, for nature, for the mountains, for old age, even for death. You may not have noticed, but reverence is gone from our contemporary American culture. Osler said the good physician needs aequanimitas. I would add to that a few gray hairs, courtesy, an ability to listen, a clean lab coat, and some reverence for the individual dignity of his patients. Patients, in turn, want to revere their doctor—why else risk their life in his hands? We should be attentive to that need.

Old age is revered in parts of the East. Why not in the West? Is it part of our general loss of reverence for anything, or more of a denial of the inevitable? Death is also considered an enemy. Could it be that the Westerner who *must* know the answer to everything is made insecure and uncomfortable by the uncertainty about what death means? Science knows nothing of the meaning of death and never will. We can't figure it out with facts and numbers. Death is a mystery. The mystic shouts "hooray" and the Westerner turns away. Medicine must not turn away. We can help ourselves and our patients by treating old age and death with more attention and reverence—not for the physiology, but for the mystery. Thank goodness there is inevitable death; the alternative is too gruesome to contemplate. Once again we can learn from our Eastern cousins, most of whom look on death as release or opportunity. Our Judeo-Christian heritage teaches that too, I think, but it's not much talked about.

In this rapidly changing world, we seem to be running ever faster and working ever harder toward goals that are becoming ever more nebulous. The traveling Westerner (and that includes most Japanese) sees the world through the aperture of his camera, fixing and measuring it for the permanent record so that he and his wife can argue over whether that building was the Temple of Heavenly Bliss or the Palace of Eternal Enchantment the next time they show their slides. When bird song fills the evening air, it somehow seems important to know whether the singer is a rose-breasted nightingale or a double-breasted seersucker. What does it really matter? Why do we have to name, record, and analyze (reduce) everything? Serenity, tolerance, patience, humility, perspective, wonder, and humor seem more at home in the East than the West. Have they any place in Western medicine? They are certainly not scientific. What if, instead of

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working harder, we relaxed a bit? If we slowed down, would our priorities sort themselves out better? If we worked less frantically, would the world be different or even notice? I doubt it. If we did less and contemplated more, would *we* be different? I suspect we would.

Another "Eastern" trait is to take the long view and to be a bit more doubtful than the Westerner about "progress." The convulsions now going on in medical economics, regulation, and practice seem overwhelming to us. The sky is falling. Things will never be the same again. Think for a moment about the Chinese professionals whose lives were turned upside down by the Cultural Revolution in the 1960s. Then, a decade ago, they were restored to grace. Now their fate is uncertain again. They remain cautious, their enthusiasm well in hand. Present circumstances may also change. The rapid political shifts of China's last 50 years are indeed astounding, but in the perspective of 4000 years of history, they are as a pimple on the face of time. The wise Easterner knows that this too shall pass. The pendulum swings back and forth.

The Eastern calendar suggests a cyclic nature to human history. Their religions advocate patience, return to nature, even resignation from what we would call worldly responsibility. Some Easterners do withdraw from the battle, leave society, and retire into mystical meditation, but most do not. Look in your laboratories and in your university classrooms or read the financial pages, and you will find enormous evidence of intelligence, industry, and purpose from our Eastern cousins.

The West, however, believes in continuous progress. We must participate. We must try to fix everything. Progress is inevitable if only we work hard enough. Activism is the answer. A cynic might say that the American wants to fix everything, the European thinks that nothing is fixable, and the Easterner doesn't believe it matters whether it is fixed or not. There must be a middle ground that could find satisfaction in useful work not entirely concentrated on making money, winning the Nobel prize, or changing the world by next Wednesday.

There is a cyclic nature to human activities. Progress is not unidirectional. Oat bran is "in" today, but you know it will be something else tomorrow. Fashions and fads come in medicine as they do in our music and politics. The restlessness, adventurism, and enthusiasm of youth always want to change things. Faculties are always tinkering with curricula, but an observer with a long view often notes similarities of the new to the old.

I am amused when the college and medical students whom I am privileged to interview express enthusiasm about the brand-new and growing concern for ethical issues in medicine. Many have never heard of Athens, and almost none realize that there were complex ethical systems in place in China long before Plato. Is medicine really as progressive as we like to think? Or is there an important central core that is timeless?

Certainly the scientific and technologic components of medicine have progressed a bit, but goodness gracious, there is a lot we do not know about common diseases, even now. Our membership in this august Society recognizes our great talents and our leadership role in the advance of medicine, but who can tell me the true cause of a single noninfectious disease of the gastrointestinal tract? Can anyone explain to me why some persons get pancreatitis, duodenal ulcer, inflammatory bowel disease, gastrointestinal cancer, or even appendicitis and gallstones when most persons do not? Or, for that matter, why some of these diseases get better without our attention? We haven't quite got the complete answers yet to a lot of problems. We have much to be humble about if we take off our rose-colored glasses. Humility sounds more like an Eastern virtue than a Western one, though, doesn't it? Much of our culture does not even consider humility a virtue.

I do believe there is a timeless central core to the practice of medicine and surgery, a core of extrascientific knowledge, art, and wisdom that deserves more attention than it gets in the West today. Our attentions have been so distracted and warped by the constant bombardments of a market- and media-driven, technology-oriented culture that we have confused our priorities. For example, the orgy of measurement that characterizes most intensive care units often distracts us from asking the important questions. Sometimes we even forget to ask the patient how he or she feels. Collecting data is less threatening to us than facing difficult questions or decisions. Being busy is more comfortable than being thoughtful.

Much of our practice does indeed involve the enlightened use of technology and the manipulation of current scientific data to make treatment decisions. Specialists in Medicine are particularly devoted to this intellectual type of activity and would rush to agree with me that surgery is not nearly as cerebral a pursuit. Too bad for them, though, I would say. They're missing most of the fun. The doctor who, in his enthusiasm for images, measurements, and the "literature," neglects the individual human variables of his patient is a fool.

Where science touches man it turns to art.

JOHN CIARDI

Since Imhotep of ancient Egypt, the core of medicine has involved a one-on-one shared involvement of patient and physician in matters of life and death. What could ever bring us closer to other human beings than to be mutually involved in life-threatening and, hopefully, life-preserving problems? War, childbirth, and only a few other activities share this bond. Risk, devotion to duty, and all-consuming responsibility add to the burden and the glory. Indeed, there is a glorious satisfaction that comes with a successful outcome of a desperate trial experienced, indeed suffered, by patient and surgeon alike and together. If we neglect the one-on-one personal relationship between patient and physician that is the permanent core of medicine, our profession will die. If we preserve that core, even though the technologies, economics, and politics may be everchanging and swirl around us, we shall be safe and happy and can continue to be proud of our esteemed role in this society of man. Yet the question most often asked by patients in a modern hospital today is not "What is my diagnosis?" or "What is the appropriate treatment?" but rather "Who is my doctor?" The patient does not mean who is it that can explain the significance of the elevated laboratory test; he wants to know who cares enough and who feels responsible enough for him personally to assist his safe passage through the impersonal indignities of modern diagnosis and treatment.

It is not the science, not the money, not even the peer respect that motivates us to work all night against heavy odds. Rather, it is the wonderful privilege of using skill and knowledge to bind us to our fellow man in something more important than commerce, sociability, and the daily activities of life. Surgery is an adventure with all of the positive connotations of that word, but a perilous one, not to be undertaken by the foolish, the uninformed, or those seeking fame or fortune. To risk another's life is a heavier burden than to risk one's own. Those who do not share that sensitivity do not deserve the privilege—nor, indeed, will they ever experience the full satisfaction of our profession.

I am not really against science. In a very positive way, it distinguishes Western from Eastern culture and properly dominates the formal education of our doctors-to-be. It is a tool of medicine, however, not a master. We tend to forget that the only certain thing about "scientific truth" is that it will change when the next bits of data come in. I will admit, however, to concern about the potential for future neglect of the human side of medicine by a profession dominated, even bullied, by concentration on advances in science and technology. Absolute devotion to science may have obscured our insight into many medical problems and at times may have distanced us from patients who have needed our nonscientific skills.

Each of us has been showered with gratitude for our devotion and understanding care to a terminally ill cancer patient and his family. In fact, the good physician may do more for his patient who dies than for the one who lives. But how many times have you been thanked for referring a patient to an investigative protocol? Our scientific side says "yes" to the protocol; our nonscientific side says "no." What should we do? There is ambivalence here and paradox. Once again, the Western mind does very poorly with either.

A few years ago, I had the privilege of lunching in a Shanghai hospital with a leading liver cancer surgeon whose scientific pioneering efforts are respected worldwide. We ate turtle stew. He told me that he often prescribed turtle for his unresectable patients. He was confident that it helped. Earlier that same morning, his anesthetist wife had lectured us on the benefits of her field of acupuncture. My Western mind was terribly troubled by this untidy potpourri of therapies, but, on reflection, it finally occurred to me that the problem was mine and not his.

Maybe a little less action, less progress if you will, and a little more contemplation and observation might substitute nicely for another battery of tests or procedures. But, of course, in our culture we cannot withdraw from the action. Our very nature as surgeons demands an active role. If we did not believe in active treatment, if we did not believe that what we do as doctors made a significant difference to most patients, there would be much less satisfaction in medicine. Doctors want people to get well, patients want doctors to make them well, and mostly patients get well—giving credit to the doctor—a very nice arrangement that works for the Chinese herbalist as well as for the Western endocrinologist. It is not a very scientific arrangement, but it is a very useful one nonetheless. That is why protocols with a no-treatment arm are so unpopular. First, the results are too humbling, and second, both patient and doctor miss the emotional kicks that are such an important part of medicine.

The down side of this is that everything that comes along gets tried as a new therapy. Faith makes much of it seem to work, but only science can eventually sort it out. In the meanwhile, for most practitioners, a healthy doubt and a happy irreverence for novelty seem appropriate. The laser and the lithotriptor may solve most of man's ills, and interleukin 2 may do the rest, but the long view would counsel us not to bet on it. The desire for novelty is an effective marketing strategy, but not a sound medical one. Slow acceptance of unproved therapies will more often protect our patients from harm than it will deny them opportunity for benefit.

So, my call is not for nonactivism or nonparticipation, but rather for a more thoughtful selection of how we might spend our energies. Practitioners fret nowadays about the hassles of practice, the loss of control and autonomy, the inundation with regulation, and the piles of paperwork. We do not really *have* to participate in competitive marketing, in the triumph of technology over common sense, in the rush to quantify quality, and in the daily massage of immature discoveries by a meddlesome media. We do not *have* to participate in all those unpleasant diversions that increasingly take us away from our patients. What if we just said "No, thank you" to the do-gooders and to the hucksters? What if we just concentrated on relieving suffering? Your Western instincts rise up to protest that if we do not participate in the marketing decisions, someone else will control our profession and do it badly. I doubt this. The combination of magic, humanism, and science that medicine represents is too important to the educated public to be left to the nondoctors to organize and control. The regulators may limit the number of Rolls Royces we can buy, but they will not control a profession characterized by responsible service devoted to excellent patient care. Laissez-faire has many drawbacks, but who has not seen tincture of time do better than multiple committee meetings or multiple invasive procedures in solving a difficult problem? Detachment is different from neglect. Patience is not the same as indifference. Goodness, those are hard lessons for a surgeon to learn. But if we learn them, the doctors of the future may practice in a less aggressive, less antagonistic, more civilized environment that will provide fewer distractions from the central business of relieving suffering.

Let me perhaps offend or perplex some of you by suggesting that both the economic consequences of the current rapid changes in health care financing and the infusion of more women into medicine will bring us back nearer to where we ought to be. Too much money has ruined a lot of good doctors. Financial incentives have altered their practices, and the need to deal with all that excessive gain has diverted their attention from the joys and responsibilities of bedside care. Surely, if we practice good medicine, the competent physician will earn a comfortable income in the future—comfortable enough to afford, perhaps not all of the luxuries, but all of the necessities of life, including the education of his children. Surely, the influx of women will bring more caring and less macho to a profession that needs more caring and less macho. Society will reward us comfortably if we continue to earn its respect by insistence on quality and if we learn to appreciate that the responsibility for financial and even ethical matters must be shared with patients and society at large.

Medicine is a high mountain to climb. It requires enormous energy, patience, knowledge, hard work, experience, and skill. The correct answers to the right questions are ever changing, and so are the challenges. No wonder we attract some of the best students who persist in being more interested in quality than quantity. Surgery has the best of it. We add to the challenges just mentioned more risk, more adventure, more closeness to life and death, more craftsmanship, and the wonderful camaraderie of the operating room.

If we do not fly too high, if we focus on essentials, if we remember that courtesy and kindness are as important as science in the treatment of the individual patient, if we recognize death as the ultimate healer and that social and economic conditions are cyclical bothers that surely will change if we keep a long perspective, if we reject hype and sham—in short, if we learn a bit from our Eastern colleagues about attitudes, particularly about the difference between quality and quantity, we may have less to worry about in the future. I read a book recently that described the advent of neon lights, Rambo, and rock music in Kathmandu and other Eastern cities as evidence that Western culture was taking over Asia. The book, however, ends with a reverse twist by wondering whether the huge influx of Asian students and Asian capital into the West might bring with it some Eastern values. It wouldn't be all bad.

When you walk in the quiet of the Himalaya, each person whom you pass on the trail nods his head, clasps his hands, and says, "Namasté." The word is like the Hawaiian "aloha"—both hello and goodbye, have a nice day, and God be with you. There is reverence and courtesy here, respect and gratitude as well. I thank you for the great honor of presiding over this Society for 1 year and for your kindness in listening so patiently. Namasté.

Hydrocortisone Rapidly Induces Aortic Rupture in a Genetically Susceptible Mouse

Jeffrey M. Reilly, MD; Edward B. Savage, MD; Colleen M. Brophy, MD; M. David Tilson, MD

• The Blotchy mouse has an X-linked trait that leads to aortic aneurysms and subsequent fatal rupture in nearly all affected male mice. Heterozygous female mice occasionally develop aneurysms, but they rarely rupture. Ten heterozygous female mice received 0.45 mg/mL of hydrocortisone acetate in drinking water. Within 2 weeks, 9 of 10 mice were dead (6 with proved aortic rupture, 3 with presumed rupture). The 10th mouse was documented to have an aortic aneurysm. A dose-response curve was generated. Hydrocortisone's effect was shown to be dose-dependent. In another experiment, normal female mice received 0.10 mg/mL of hydrocortisone acetate for 14 days. Two mice developed aneurysms, and the others developed aortic ectasia. These experiments establish the role of hydrocortisone in the induction of aortic rupture in a mouse with genetic susceptibility and the induction of aneurysms and ectasia in normal mice.

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The Blotchy mouse serves as an animal model of aortic aneurysms. It has an X-linked trait, which results in the development of fatal aortic aneurysms in nearly 100% of the affected male mice.[1] Thirty-seven percent of heterozygous female mice, ie, those with one normal and one abnormal allele, develop aortic aneurysms and/or ectasia; but they rarely, if ever, die of aortic rupture.[1] The biochemical basis of this defect is thought to be due to deficient copper absorption from the gastrointestinal tract, leading to systemic copper deficiency.[2] This, in turn, results in decreased activity of the copper-dependent enzyme lysyl oxidase, which is responsible for the cross-linking of elastin and collagen.[3]

In animal models utilizing either hamsters or turkeys, several different types of steroids have been shown to induce aortic dissection or rupture in one third to two thirds of the treated animals.[4-8] The purpose of this investigation was to determine if hydrocortisone acetate would influence the development of aortic aneurysms and/or rupture in heterozygous Blotchy mice.

METHODS

C57BL/6-J Blotchy mice were obtained from an inbred colony maintained at the Yale Medical School, New Haven, Conn.[9] Twenty heterozygous female mice were randomly assigned to either the control group or one of three experimental groups in the first phase of the study. One experimental group received 0.45 mg/mL of hydrocortisone acetate (Sigma Corp, St Louis, Mo) and 750 mg of tetracycline hydrochloride (Sigma Corp) in drinking water. (The tetracycline was added to prevent septic complications.) A second experimental group received the same regimen plus heparin sodium at 200 U/mL in drinking water. The third group received only heparin. (Heparin was used because in an antiangiogenesis regimen utilizing hydrocortisone and heparin, some mice have developed aortic aneurysms [J. Folkman, MD, oral communication, July 2, 1983].) The control group received tetracycline. There were five animals in each group. All groups had ad libitum access to drinking water, and the mice consumed on average between 5 and 10 mL per day. During the course of the experiments, the mice all received standard laboratory chow. To limit infectious complications, the mice were kept in filter-frame cages; masks and gloves were worn by laboratory personnel when handling the mice; all food, water, cages, water bottles, and bedding were autoclaved; and cages were changed twice per week. Mice that died in the course of the experiment were autopsied, and specimens of the heart and aorta were prepared for histologic examination. Cut sections were stained with hematoxylin-eosin and elastin–van Gieson stains.

In the second stage of the experiment, four experimental groups, each with six heterozygous mice, were given 0.45, 0.30, 0.15, and 0.045 mg/mL of hydrocortisone acetate in drinking water. All groups also received tetracycline as in the first portion of the study. One animal from each group was selected randomly and was killed for angiography and histologic examination. These animals were not used for statistical analysis of survival. Angiography was performed by instillation of 1:1 diatrizoate sodium and diatrizoate meglumine (Renograffin) to normal saline into the left ventricle.

A third experiment with normal C57BL/6 female mice was also carried out to provide additional control data. Eight animals were given 0.10-mg/mL doses of hydrocortisone acetate in drinking water for 14 days. An additional eight female mice served as controls. All of the mice were killed, and the left ventricles were injected with latex to facilitate examination. Aortic diameter was measured using microcalipers.

RESULTS

Stage 1: Short-term Study of Blotchy Female Mice

In the first phase of the study, all 10 of the mice receiving tetracycline alone or heparin and tetracycline (5 animals were in each group) were alive at the end of 30 days unless killed for analysis. Nine of the 10 mice receiving hydrocortisone were dead by day 15. Heparin had no influence on survival. The lone survivor was killed for angiographic study on day 16. Of the 9 mice that died, autopsy was possible on 6 (the other 3 had been cannibalized by the surviving mice). Aortic rupture was present with hemothoraces in all 6 mice autopsied. Precise

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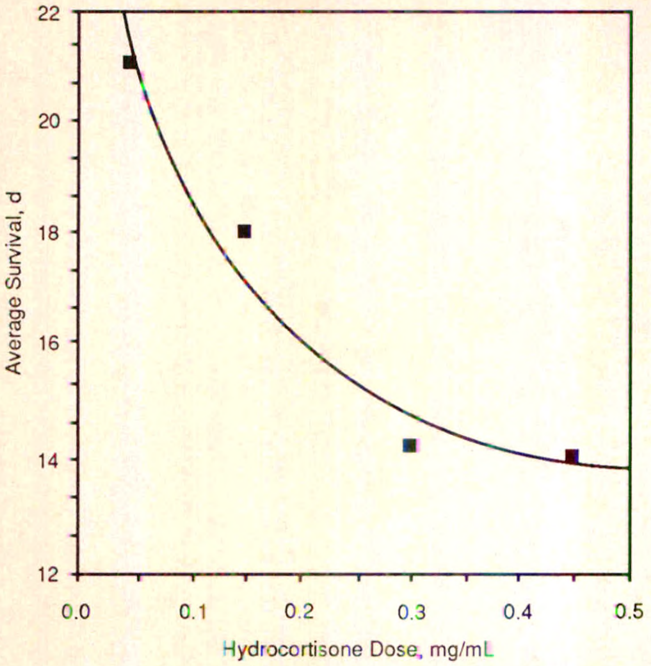

Average length of survival of treated mice that died of aortic rupture at varying doses of hydrocortisone acetate during the 21-day study period. The squares represent the average length of survival at each dose.

determination of aortic diameter was not possible because this relies on the injection of latex under pressure into the intact aorta. Of the 3 mice mutilated, 1 died early in the study, but the other 2 died on days 11 and 12, which was the time that the other mice were dying of aortic rupture. The angiogram of the surviving mouse revealed a fusiform thoracoabdominal aneurysm, as well as carotid ectasia. Histologic sections of the aortas studied were remarkable for disrupted elastic laminae at the site of rupture, with extravasation of blood. Otherwise, the sections were similar to control aortas.

Stage 2: Dose-Response Curve

In the second portion of the experiment, a dose-response curve was generated, and the mean survival was calculated at each dose. The dose-response curve is shown in the Figure. The effect of hydrocortisone was shown to be dose-dependent.

Stage 3: Normal Mouse Experiment

There were two aortic aneurysms noted in the experimental group and none in the control group. The mean aortic diameter in the steroid group (1.86 ± 0.25 mm) was twice that of the control group (0.93 ± 0.23 mm) ($P<.001$).

COMMENT

This study demonstrates that hydrocortisone rapidly induces aortic rupture in mice with a genetic predisposition to aneurysm formation. We believe that the mice most likely died of rupture of aortic aneurysms, but our autopsy data are not complete enough to state this definitively. This effect is dose-dependent. This study also demonstrates that aortic aneurysms and ectasia can be induced in normal mice. The mechanism by which this occurs has not been established. Heparin appeared to have no influence on survival. It was used empirically in this trial because J. Folkman, MD (oral communication, July 2, 1983), had reported to us that an antiangiogenesis regimen containing both heparin and steroids induced aortic rupture. We used both to determine which agent was responsible for this phenomenon.

Aortic dissection and aneurysm formation have been observed in hamsters treated with cortisone acetate.[8] Hamsters were treated with cortisone to accomplish heterologous transplantation of human fetal lung tissue, and it was noted that many animals died of massive intrathoracic or intraperitoneal hemorrhage. Histologic examination revealed that the hemorrhage was due to rupture of an aneurysm of the aorta. Subsequent investigations revealed that aortic rupture could be produced in hamsters within a few days to 1 month, depending on the dose of corticoids employed.[6] In an antiangiogenesis regimen in mice that included hydrocortisone, spontaneous aortic rupture has also been observed (J. Folkman, communication). In turkeys treated with diethylstilbestrol, 14 of 24 died within 2 to 5 weeks.[4] In these studies, approximately one third to two thirds of the experimental animals developed aortic dissections and/or aneurysms, in contrast to the nearly uniform induction of aortic rupture in the present genetically predisposed animal model. In normal mice, we observed no aortic rupture, but a full dose-response curve was not determined.

The mechanism by which steroids induce aortic aneurysms and/or rupture is unknown. Glucocorticoids are known to produce impaired wound healing, decreased inflammation, osteoporosis, lymphoid tissue regression, and dermal atrophy.[10] Steroids are also known to result in salt retention and hypertension, although rupture of aneurysms has been shown to occur without an increase in blood pressure in a hamster model.[6] It is possible that hypertension may have played a role in the development of aneurysms and aortic rupture in the present experimental model. Steroids are also known to decrease collagen synthesis,[10] but the rapidity with which these mice developed aneurysms suggests that a factor(s) in addition to decreased synthesis may play a role, since elastin has been reported to have a half-life as long as 40 years in rodents.[11]

Aortic aneurysms have been noted to occur in various diseases commonly treated with corticosteroids. Corticosteroids administered for Dressler's syndrome after myocardial infarction have resulted in delayed healing and the formation of ventricular aneurysms.[12] In patients with Kawasaki's disease, 65% of those treated (with steroids) develop coronary artery aneurysms compared with 20% in untreated controls.[13] Pregnancy, a state of increased physiological levels of steroid hormones, is associated with aortic dissection,[14] cerebral aneurysm rupture,[15] and rupture of visceral artery aneurysms.[16]

The association of aneurysms with the various forms of vasculitis is also interesting. Progressive widening of the mediastinum with aneurysmal dilatation of the aorta and aortic regurgitation has been reported in seven cases of giant cell arteritis, a generalized large-vessel arteritis treated with high doses of steroids.[17] Aneurysms have also been reported to occur in association with Takayasu's arteritis.[18]

The present data suggest that hydrocortisone induces aortic rupture in a mouse genetically susceptible to aneurysm formation, as well as aortic ectasia and aneurysm formation in normal mice. There is also evidence in the literature that aortic aneurysms occur in association with high-dose steroid use. Considering these facts, we propose that the risk of aortic rupture and aneurysm formation may be added to the growing list of complications of steroid therapy. Prospective studies with serial ultrasound examinations and chest roentgenograms in patients administered high-dose steroids will be needed for a definitive answer on the effect of steroids on the development of aortic aneurysms in humans.

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Discussion

ROBERT W. HOPKINS, MD, Providence, RI: Dr Reilly carefully emphasized that these observations apply to the heterozygous female Blotchy mouse and not necessarily to humans and that there are obvious reasons for differentiating this model from aneurysms in humans. These experimental aneurysms develop in days to weeks, and those in humans develop over many years. I wondered about a possible predisposition of patients with Cushing's disease to develop aortic aneurysms, so I called Dr C. A. Wang; he was not aware of such, nor am I. We all, however, know of anecdotal situations where steroids seem to have played a role in expansion or rupture in humans. There are other good reasons to consider the effects of steroids on atherosclerotic aneurysms in humans. Dr Reilly's collaborator, Dr Brophy, discussed the histopathologic features of aortic aneurysms in humans, emphasizing the destruction of the elastica (noted by Dr Reilly in this report) as well as the effects of the inflammatory process. In humans, there is also extensive replacement of smooth muscle by fibrous tissue. In accordance with Laplace's law, the wall tension of an aneurysm four times the normal diameter, for example, is four times normal. With pulsation stretching the wall, trauma—at least microtrauma—must occur frequently, necessitating frequent repair. Dr Reilly speculated on the effects of steroids on the elastica. Steroids also affect collagen synthesis, deposition, and remodeling, tending to inhibit some repair processes.

In addition to the disruption of the elastica in these animals, is smooth muscle similarly affected in this or other Blotchy mouse models? Do you think that collagen and fibrous tissue in aneurysms in humans may also be adversely influenced by the effects of the steroids?

DONALD J. GLOTZER, MD, Boston, Mass: I would like to know whether you had aortic aneurysm ruptures in the Blotchy mouse at clinically relevant doses comparable with even the astronomical doses of steroids our internist friends commonly use for some of the conditions that you mentioned.

DAVID W. BUTSCH, MD, Montpelier, Vt: How safe was your presumption that three of the nine mice that died actually died of aneurysms, since that assumption forms an important part of your conclusions? The fact that no autopsy was done raises the question of whether some mousy lawyer got to the evidence first!

DR REILLY: To address Dr Hopkins' question about the histopathologic features, particularly in the histochemistry of the smooth-muscle cells, the smooth-muscle cells appeared to be essentially normal in the mice that were treated with hydrocortisone, with the only abnormality being that they tended to be slightly pleomorphic. We do not see the dropout of smooth-muscle cells that has been postulated to occur in abdominal aortic aneurysms. It should be emphasized that this animal model is not really a model of abdominal aortic aneurysms so much as of thoracic aortic aneurysms. Probably the closest human model to this would be the type of aneurysms seen in patients with Marfan syndrome, who have a disorder of connective-tissue metabolism and frequently develop ascending thoracic aortic aneurysms.

Concerning the role that collagen and fibrous tissue play in the development of aneurysms, I think that in terms of steroids, there are, as Dr Hopkins said, anecdotal reports in the literature of patients with various collagen vascular diseases treated with high-dose steroids over periods of years who actually develop thoracic aortic aneurysms. However, most of these reports focus on the primary disease and not on the steroid therapy. So, it is really purely speculation on our part as to whether steroids are playing a role.

In terms of Dr Butsch's question concerning the findings in 3 of the 10 mice, the interesting thing about mice is that they are cannibals and if 1 of them dies in a cage, they will eat each other. The presumptive evidence of aortic rupture in this group is that the mice were found at autopsy (complete autopsy was not possible because often some of the thoracic contents were eaten) to have very pale livers, and it appeared that their vascular volume had been completely depleted, so it was consistent with aortic rupture. However, even if these three mice are removed from the statistical analysis, the incidence of aortic rupture in this group is still significant.

The last question referred to the dose-response curve and whether there were any ruptures at the lower rate. The answer is yes. At varying doses, there were no aortic ruptures in the groups only at the lowest dose, which was 0.045 mg/mL. At all the other doses, aortic rupture occurred. The incidences reached 100%, however, only at the higher doses.

Gallstone Lithotripsy vs Cholecystectomy

A Preliminary Cost-benefit Analysis

Janice G. Rothschild, MD; Ryan F. Holbrook, MD; Randolph B. Reinhold, MD

• From July 1988 to January 1989, we compared the course of 48 patients undergoing elective cholecystectomy with that of 18 undergoing extracorporeal shock wave lithotripsy for symptomatic cholelithiasis with respect to treatment, hospitalization, recovery, and cost. For elective cholecystectomy, average length of surgery was 76 minutes (range, 31 to 186 minutes); average length of stay was 4 days; total cost was $6240; morbidity was 10%; and return to work averaged 5 weeks. Average extracorporeal shock wave lithotripsy treatment length was 136 minutes (80 to 158 minutes); average length of stay was 2 days; total cost was $5921; and hematuria and petechiae were seen in 33% and 28%, respectively. Re-treatment cost was $4880. All of these patients were active in 24 hours; return to work averaged 3 days. As results of the Food and Drug Administration study are still pending, recurrence and re-treatment rates are unknown. We conclude that extracorporeal shock wave lithotripsy is less costly, initially, with further reductions probable when performed on an outpatient basis. Though re-treatment may be required, return to normal activity is dramatically shortened.

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Tait's 1885 assertion that "Amongst all the many advances which modern abdominal surgery has seen, I claim there is none so certain nor so free from risk and so brilliantly successful as the surgical treatment of gallstones"[1,2] is being challenged on grounds that alternative treatments can provide symptom relief, are freer from risk and perhaps more brilliantly successful. To assess claims and perhaps allay fears, our early experience with biliary lithotripsy led us to undertake a concurrent comparison of extracorporeal shock wave lithotripsy (ESWL) with elective cholecystectomy (EC) in the treatment of symptomatic cholelithiasis.

PATIENTS AND METHODS

During the 6-month period from July 1988 to January 1989, 64 patients were treated for symptomatic cholelithiasis at the New England Medical Center, Boston, Mass. There were 50 women and 14 men, with an average age of 44 years (range, 19 to 78 years). Based on patient preference and entry criteria (fewer than three stones, ≤3 cm, in a functioning gallbladder), 46 patients underwent EC and 18 underwent ESWL as part of a 10-center Food and Drug Administration (FDA) trial. We concurrently compared the courses of these two groups with respect to presentation, evaluation, in-hospital course, and length of stay, as well as complications, costs, and recovery. Six- to 12-month follow-up was obtained with respect to recovery, symptom resolution, and need for further hospitalization or treatment.

RESULTS

EC

Forty-six patients (37 women and 9 men) underwent EC. Both groups' characteristics were as follows (where ASA indicates American Society of Anesthesiologists physiologic grade):

	EC	ESWL
Sex, %F	80	72
Age, y (range)	44 (19-78)	41 (26-58)
ASA I, %	35	83
ASA II, %	50	17
ASA III, %	13	0
ASA IV, %	2	0

All patients presented with pain; presenting symptoms (percentages) were as follows:

	EC	ESWL
Pain	100	100
Postprandial pain	85	61
Nausea	54	72
Vomiting	41	39
Fatty food intolerance	52	56
1 y duration	39	72

Forty-one percent of patients undergoing EC had noted symptoms for less than 6 months, 39% for greater than 1 year; and 39% of patients were symptomatic on a daily or weekly basis. Four patients had been previously hospitalized for biliary symptoms and treated with analgesics or intravenous antibiotics and bowel rest.

Ninety-eight percent of patients undergoing EC had an ultrasound done as part of their initial evaluation. This showed multiple stones in 84%. Only 13% showed one to three stones. Other radiologic examinations included oral cholecystography in 15%, abdominal flat roentgenograms (kidney, ureter, bladder scans) in 54%, and hepatobiliary scanning in 22%. Laboratory values revealed normal complete blood cell counts, liver function test results, and amylase levels in 85%, 59%, and 81% of those measured, respectively.

All patients in this group underwent cholecystectomy; one

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patient underwent a concurrent panniculectomy, and one a ventral herniorrhaphy. Seventy-four percent of patients were taken to the operating room on an admit-after-major-surgery basis. Forty-six percent of patients carried a concurrent medical diagnosis. All operations were done using general endotracheal anesthesia. The average length of surgery was 76 minutes (range, 31 to 186 minutes); average length of anesthesia was 111 minutes. No patient required transfusions, and there were no intraoperative complications.

The average length of hospitalization was 4 days (range, 1 to 15 days; mode, 2 days). Patients were eating a regular diet within an average of 2 days. Complications occurred in five patients, lengthening hospitalization in three. These included urinary retention in one, a urinary tract infection in a patient with an indwelling Foley catheter, interstitial nephritis in a patient with sickle cell anemia, recurrent pericarditis in a patient who had had a pericardiectomy, and multiple premature ventricular contractions, not requiring treatment, in one patient. One patient required early rehospitalization for pain control and nausea and one for evaluation of a pancreatic abnormality noted at operation.

In the absence of specific indications, our policy is not to perform intraoperative cholangiography. Only two patients required intraoperative cholangiography for a history of hyperamylasemia. Both studies' results were normal. No patient in this elective group required common bile duct exploration. With the removal of the gallbladder and absence of signs or symptoms at 6 to 12 months (all patients were contacted for follow-up), patients were deemed stone free.

The average cost of hospitalization was $6240, including all professional and surgical fees as well as in-hospital costs. The largest segments of the cost accrued to hospital room and operating fees, as follows:

	EC	ESWL
Professional	1146	1500
Operating room	1593	2000
Recovery room	340	800
Anesthesia	371	0
Roentgenography	126	419
Laboratory	249	140
Medical supplies	230	12
Pharmacy, intravenous	507	275
Room	1472	775
Other	206	0
Total	**6240**	**5921**
Total including re-treatment	6240	8100

Patients returned to work at an average of 5 weeks. They were driving within 3 weeks and felt they were back to normal baseline within an average of 6 weeks. Sixty-five percent were asymptomatic (at 6 to 12 months), 21% improved postoperatively, and 72% were eating normally. The average number of postoperative visits was one, with postoperative professional and laboratory fees billed separately.

ESWL

During this period, corresponding to our first 5 months of experience with biliary lithotripsy, 18 patients underwent ESWL for gallstone fragmentation. There were 13 women and 5 men. Their characteristics and presenting symptoms are given above. None had symptoms for less than 6 months. Twenty-eight percent were symptomatic on a daily or weekly basis.

No patient had been previously treated or hospitalized for biliary symptoms. Pretreatment evaluation included ultrasound and 12-pill oral cholecystography, as well as abdominal flat roentgenograms (kidney, ureter, and bladder scans) in all patients as required by FDA protocol. Forty-five percent of patients had a single stone, 33% had two stones, and 22% had three stones. All patients had complete blood cell counts, amylase levels, and liver function test results measured, and all of which were normal.

Patients underwent ESWL using the Dornier MPL 9000 as described by Sackmann et al.[3] The average length of treatment was 136 minutes (range, 80 to 158 minutes). The average number of shock waves delivered was 1174 (range, 687 to 1500). Eighty-nine percent of the procedures were done with intravenous sedation, generally less than 50 mg of meperidine hydrochloride (Demerol) and 2 mg of midazolam hydrochloride; the remainder were done with no anesthesia. One patient suffered a respiratory arrest related to her sedation, which was reversible with naloxone hydrochloride (Narcan).

The average length of hospitalization was 2 days as required per protocol. Besides the intraoperative respiratory arrest mentioned above, seven (excluding respiratory arrest) patients suffered complications; five had cutaneous petechiae and six had microscopic hematuria. Complications were neither clinically significant nor did they prolong the hospital stay. There were no deaths.

The average cost of hospitalization was $5921, including technical and professional fees and in-hospital testing, as tabulated above. These figures were calculated using current renal lithotripsy figures, with technical cost inserted as "operating room" and day-surgery suite costs as "recovery room."

Study patients were randomized to receive a double-blinded study drug starting 1 week before treatment, for 6 months. Half received ursodeoxycholic acid (Urso Falk) and half placebo. The cost of a 6-month course of the approved bile acid would be calculated at $529, for an average medication cost of $265 during the course of this study (included in "pharmacy" in the above tabulation). There was no discernible difference in the tolerance of the two groups with the exception of mild, self-limited diarrhea at the onset of therapy in a few.

Seven patients required rehospitalization for re-treatment and one for severe biliary colic. One patient required cholecystectomy because of inability to localize his stones. Of the 17 patients followed up, 6 (35%) were rendered stone and fragment free. Eleven (65%) were noted to have residual fragments in follow-up studies. Hospitalization for re-treatment averaged $4880, bringing the average total cost for the ESWL-treated group to $8100.

Patients were eating within 1 day, back to work in less than 3 days, driving within 2 days, and back to normal activity within 6 days, on average. At 6 to 12 months after treatment, 44% were asymptomatic, 44% were improved, and 72% were eating normally. All patients had three postprocedure visits within 6 months, with obligatory ultrasound, laboratory testing, and cholecystography as required by the FDA. Posttreatment follow-up testing and office visits would be billed and calculated independently.

COMMENT

Cholecystectomy has been the treatment of choice for symptomatic cholelithiasis for 107 years. Its worth must be evaluated on the basis of operative morbidity and mortality, relief of symptoms, and patient acceptance as a treatment modality. Questions of hospitalization time and cost that have arisen within past years are becoming increasingly important. Length of disability and time away from work need be factored in as well.

Data regarding the safety of cholecystectomy have been accumulating for 50 years. Multiple series confirm a mortality with EC of 0.5% to 1.5%.[4-7] Mortality in these series was due to specific postoperative complications in less than 50%; more often it was due to the cardiopulmonary status of the population, with mortality increased in the elderly and in the acute setting. Our series, reflecting only truly ECs in a mixed population, was without mortality.

Morbidity data parallel this trend. Larger series show major morbidity at less than 5%. Less than half of the complications are related to the surgery per se, with sepsis, wound, and subhepatic being the most common in 3% to 7%.[4,5,7,8] Postoperative morbidity is more often related to pulmonary and cardiovascular disease. Again, acute intervention in the elderly population carries a higher morbidity. Our population represented a spectrum in age and comorbidity, with 15% designated ASA III and IV, 46% having associated medical diagnosis, and 59% older than 40 years. Our series is consistent with minimal nonbiliary morbidity.

Only in more recent series have issues of length of stay been addressed. While there have not been significant changes in 30-day morbidity figures, more recent data have shown that many of the "standards" associated with cholecystectomy, including nasogastric decompression, prolonged nonoral nutrition, and extended hospitalization, may not be necessary for safe recovery.[4,9-11] Lengths of stay of 2 to 6 days are rapidly becoming the norm, and a 24-hour length of stay postoperatively is attainable.[4,9,12] This is a far cry from the postoperative course described by Langenbuch when the patient was allowed to eat on postoperative day 3 and "convalescence progressed without interruption and the patient was able to get out of bed as early as [postoperative day 12]."[13] Our series is consistent with this trend, with an average length of stay of 4 days, often less than 2 days.

Assessment of the success of a treatment modality must also include long-term results. It is clear that the success of surgery is proportional to the rigor with which the diagnosis is made. Series of common presenting symptoms[7] reveal pain as the most common presentation, followed by belching, gas, nausea, and vomiting. Specific fatty food intolerance was present in only 53%. Our series is consistent with pain as the most common presenting diagnosis; it was often postprandial but related specifically to fatty foods in only half. Nausea, vomiting, and weight loss were common presentations as well. Symptom relief with cholecystectomy has historically been in the range of 60% to 80%. Symptomatic relief was seen in the majority of our patients. Sixty-five percent felt they were asymptomatic at 6 to 12 months postoperatively, with 72% eating normally.

Of interest, and not often elicited in recent reviews, is the evaluation of posthospitalization recovery. We included the patients' perception of "getting back to normal" as well as the more objective criteria of return to work and driving. Many patients felt it was months until they were back to normal and they considered their recovery quite rapid if they were back to work within 6 weeks. This represents a less definable, but potentially much more significant, economic cost than specific financial outlay for hospitalization.

There is a segment of the population, however, to whom even these "gold standard" results are not satisfactory. These include patients to whom the idea of surgery is unacceptable because of its cosmetic results or fear of anesthesia or to whom 6 weeks without work is not tenable. With the choice for many of these patients being no treatment at all, ESWL now provides an alternative.

All our ESWL-treated patients presented with pain, 56% attributing the pain directly to fatty foods. This population tended to present later, with 72% relating symptoms for greater than 1 year, and tended to be younger, with a higher percentage of men.

The procedure is generally well tolerated, with 11% requiring no analgesia. Much of the discomfort is related to the position on the lithotripsy table. The importance of careful localization in the limitation of pain has been noted.[14-16] Piezoelectric technology may be shown to decrease pain further.[17] Our single intraprocedure complication occurred early in the series with oversedation and respiratory depression.

Sackmann et al[3] have reported a 3% incidence of gross hematuria. While hematuria is a well-documented complication of lithotripsy,[18] our morbidity is somewhat higher than previously reported, with a 33% incidence of nonclinical, microscopic hematuria. Translation of these complications to concerns of long-term effects on surrounding tissues has been raised and will require longer follow-up.[19,20]

It is clearly too early in the experience of lithotripsy to judge its ultimate symptom relief, as data regarding the FDA trial are not yet available. The experience of Sackmann, Paumgartner, and coworkers,[3,21] using stricter selection criteria, reveals an overall stone-free rate at 18 months of 84% to 91%. German data regarding long-term symptom relief using actuarial analysis reveal a 1-year recurrence of stones of 11%, leveling off at 2 years at 18%, with 9 of 118 patients suffering recurrent pain. Thirty-five percent of our patients, only half of whom were receiving bile acid treatment, were stone and fragment free at 6 to 12 months. Forty-four percent of our patients were symptom free at 6 months following the procedure, and 44% felt they were improved. In summary, from the point of view of initial morbidity, mortality, and relief of symptoms, ESWL provides a potential alternative to cholecystectomy. Data regarding long-term complications and stone-free rates await longer follow-up.[22]

A comparison of costs reveals a higher operative and technical cost for lithotripsy (as extrapolated from current renal lithotripsy fees) but markedly decreased in-hospital costs. Initial ESWL was less costly overall (90% of the charges of cholecystectomy), but inpatient re-treatment, calculated with full costs for each re-treatment, and increased cost of follow-up with its attendant additional professional and diagnostic testing fees, raise the cost considerably. In addition, recent data suggesting the need for obligatory bile acid adjuvant treatment must be added to the cost of future treatment. One would anticipate that outpatient treatment and fewer obligatory examinations would decrease cost further.

Of perhaps more significant economic consequence is the fact that the patients were back to work, without functional deficit, within 1 week of treatment. As has been noted elsewhere,[23] this, as well as the absence of a scar, further increases the appeal of lithotripsy to the general public. In our assessment of lithotripsy as an alternative treatment, we will be obliged to assess the need for continued follow-up and serial testing, as well as the likely need for re-treatment in that majority of patients who have been noted to have residual fragments in their retained gallbladders; we will also need to factor in that group who will eventually come to cholecystectomy. Whether these issues will offset the immediate economic advantage of ESWL will certainly need to be evaluated beyond the scope of this initial, preliminary assessment.[24]

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Discussion

RICHARD G. FIDDIAN-GREEN, MD, Worcester, Mass: The University of Massachusetts is 1 of 10 centers evaluating piezoelectric lithotripsy, which differs in certain respects from spark-gap lithotripsy, such as the Dornier used in the Tufts study. Our preliminary evaluation of the cost-effectiveness of piezoelectric lithotripsy is much the same as that of Dr Rothschild for spark-gap lithotripsy. We find it probably less expensive and certainly more convenient for the patients than surgery. We also find that EDAP lithotripsy is probably more cost-effective than spark-gap lithotripsy. The major differences, and we have now done some 35 treatments in our institution, seem to be that, unlike spark-gap lithotripsy, piezoelectric lithotripsy does not require admission to the hospital or intravenous medications.

Unlike Dr Rothschild's patients, most of whom received intravenous sedation, none of the patients we have treated at the University of Massachusetts have had any form of intravenous sedation or analgesia. All were free to leave immediately after the 2-hour treatment. In fact, the majority of our patients go to the cafeteria after treatment because they are starving, and most resume normal activities either that day or the next. This is in quite marked contrast to the surgical and the spark-gap recovery periods, which were about 7 weeks and 3 days, respectively, in Dr Rothschild's studies.

Professional fees are also probably lower with the piezoelectric lithotripsy as it is currently performed than with spark-gap lithotripsy, for it does not require epidural anesthesia or standby anesthesia. Another major difference is that the piezoelectric system costs about $600 000 less than the spark-gap systems and has no consumables. Evidently, one has to replace the electrodes that are generating the shock wave at the end of each treatment with a spark-gap system.

Like spark-gap lithotripsy, piezoelectric lithotripsy is effective. We have preliminary results from the EDAP study for 95 patients with single stones less than 2 cm. We have found a fragmentation rate of 94% and a stone-free rate of 34% at only 106 days. In this respect, the results of piezoelectric lithotripsy are comparable with those of spark-gap lithotripsy.

What has impressed me about lithotripsy is the relief of symptoms that many patients experience almost immediately after lithotripsy. This surprises me because patients still have fragments. Patients are often able to eat foods after treatment that they were not able to eat before treatment. The relief of symptoms may be related to the ursodeoxycholic acid. Also impressive to me is the lack of symptoms such as biliary colic, cholangitis, or pancreatitis after our procedures.

In summary, lithotripsy is a cost-effective procedure in the short term for those patients who qualify for this form of treatment for gallstones, but we have to wait and see how many of these patients have to be re-treated, and what the costs of for re-treatment and follow-up ultrasound will be.

DONALD J. GLOTZER, MD, Boston, Mass: How many patients already referred for lithotripsy were turned down? Do you have any idea of what proportion of the 65 who had surgery would have been suitable for treatment with lithotripsy?

JOHN W. BRAASCH, MD, Burlington, Mass: I hesitate to rise to speak when we have heard the strong support of the machinery people here today, but I would like to emphasize a little bit the cost of cholecystectomy. I note that most patients who are undergoing lithotripsy are asymptomatic or symptomatic and of medium or thin build; these patients are very suitable for small-incision cholecystectomy. These patients are ready to leave the hospital on the second postoperative day or the third at most. They are ready to go back to work after about 8 or 9 days and can drive their cars at 7 days. I would say that this approach to cholecystectomy, when you have good studies of the upper gastrointestinal tract, etc, and do not need to explore the abdomen, is one way to bring the cost of cholecystectomy down considerably.

RANDOLPH B. REINHOLD, MD, Boston: I am one of the coauthors. It is important to correct one statement that Dr Braasch made. None of the patients with asymptomatic cholelithiasis were treated. I think no one recommends either surgery or lithotripsy in the asymptomatic patient, though I would concur that in the young, thin adult, cholecystectomy is probably the preferable treatment over lithotripsy.

Patients in our trial had up to three stones. Obviously, you can treat any number of stones with cholecystectomy but a limited number of stones with lithotripsy.

WALTER B. GOLDFARB, MD, Portland, Me: I have just one observation, and you may answer this or not. A fee for surgeons of $1500 sticks in my craw; it is equal to or more than the surgical procedure. I wonder how that is arrived at and whether the price will go down or, consonant with medical economics, it will stay high.

C. ELTON CAHOW, MD, New Haven, Conn: I did not hear much about the function of ursodeoxycholic acid in this treatment. This really seems to be the major factor in the treatment. Lithotripsy renders the stones small enough to increase their surface area so that the cholesterol is more absorbable with ursodeoxycholic acid. How long will these patients have to be taking that? What does it cost? It was shown with the chenodeoxycholic acid studies that only 14% of those patients had stones that dissolved, and 50% recurred within 5 years. I wonder how this factors in.

STEPHEN G. REMINE, MD, Farmington, Conn: I thought this study was intriguing to someone like me who is interested in technology and how it affects our specialty. At the University of Connecticut, we have an extensive program with percutaneous gallstone dissolution. The question we are grappling with is, when is enough enough as far as the number of nonsurgical procedures that are done? Your study does not answer this and appears to be too early to evaluate the total cost per patient completely.

One of the problems I have encountered with this is trying to evaluate what our real goal is. If our goal is to compare surgery with a technology, the end points must be the same and must be more than just the elimination of the stones. All the costs associated with patient selection, subsequent problems, and re-treatments that are associated with lithotripsy must be included in the cost analysis.

Second, with the technological charge toward biliary stone disease, it challenges us as surgeons to explore other ways to improve our perioperative care, such as early ambulation. Minimally invasive surgery such as a minicholecystectomy has helped decrease hospital stays to 2 to 3 days. The standard 4 to 7 days in the hospital is no longer acceptable for biliary stone disease. So, along with the technology, we as surgeons need to explore our own techniques.

Does your study include all the costs associated with preoperative screening even for those patients not selected for treatment and for subsequent re-treatments? With limited follow-up, how valid is this cost analysis?

DR ROTHSCHILD: I will address Dr Fiddian-Green's comments first. I would agree that the largest segment of our costs was the inpatient costs. We would anticipate that lithotripsy will rapidly become an outpatient procedure. There is no question that patients are ready to leave shortly after treatment. There has been a bit of a difference in the way that each center across the country, as well as the investigators at the Boston Center, have treated patients, from having an ultrasonographer and an anesthesiologist available to having just the surgeon present. I would compare this with colonoscopy, in which a surgeon can easily sedate the patient, then send the patient to the recovery room for a short period to recover from the midazolam, to be discharged the same day. I think a standby anesthesiologist is not going to be required in the long term. I would add that for the one patient who had a respiratory arrest an anesthesiologist was present.

In reference to what Dr Reinhold was saying, 45% of our patients had a single stone and 33% had two stones. I think that differs a bit from your data and clearly will alter the stone-free rate at 6 months. We also have found that patients develop relief of symptoms almost immediately after lithotripsy. I do not think that anybody has come up with a clear indication for why that is. Even bile acid should not work that quickly.

With respect to Dr Braasch's questions, none of our patients were asymptomatic; they all had biliary colic. I would like to say that we have a routine of doing small-incision cholecystectomies. Generally, the patients go to the recovery room with a small 2-cm gauze bandage. But this has to be taken into account with the fact that 15% of our patients were designated ASA III and IV, with an age range of up to 78 years. These patients are the ones who stayed to 15 days because of concomitant cardiopulmonary or other medical problems. As both Drs Braasch and ReMine mentioned, it is our trend to send patients home the next day or the day after that. Two days, in fact, was the mode in our surgical group.

Dr Cahow, half of the patients received ursodeoxycholic acid and half of the patients received placebo as part of the double-blinded study. Data accrual in this study has been completed; data are being assessed.

I would like to reiterate that this is an initial assessment, and that we do not really have data as far as recurrence. Data regarding recurrence after medical treatment with ursodeoxycholic acid are not very optimistic. I do not have the specific figures for the cost of ursodeoxycholic acid, because that drug had been supplied during the course of the study and patients were not charged for it.

Dr ReMine, I would have to agree with you. It has been said better elsewhere that we have to be careful not to succumb to a "triumph of technology over logical thought." We are trying to get both young and older patients symptom free and avoid rehospitalizations. These listed costs did include all lithotripsy re-treatments and rehospitalizations. There was one patient who was readmitted for biliary colic several months after treatment, and those costs were factored into the totals. Also, lithotripsy follow-up is more extensive than that for cholecystectomy. Since we only started last August, this is only a 12-month follow-up.

Dr Glotzer, as far as referrals, I can only say that these 18 patients were among the 64 who were referred for treatment of symptomatic cholelithiasis. The figure in terms of the ultrasound number of stones is going to be a little skewed toward patients going for lithotripsy, but only 13% of our surgical patients had one to three stones; on the ultrasound number criterion alone, they would have been ineligible for lithotripsy.

As I noted, the fee for lithotripsy was extrapolated from the current Medicare renal lithotripsy fees in Massachusetts.

In Other AMA Journals

JAMA

Blood Pressure Changes Following Extracorporeal Shock Wave Lithotripsy and Other Forms of Treatment for Nephrolithiasis

James E. Lingeman, MD; John R. Woods, PhD; Phillip D. Toth, MD

Hypertension has been reported as a possible sequela of extracorporeal shock wave lithotripsy (ESWL). To evaluate this issue as well as the risk of hypertension following other current non-ESWL treatment options for urolithiasis (percutaneous nephrostolithotomy [PCNL], combined PCNL and ESWL, ureteroscopy, and spontaneous stone passage), detailed blood pressure measurements were made in 961 patients at least 1 year after treatment. All follow-up blood pressures were measured with random-zero blood pressure devices. This study includes 731 patients who received ESWL only (with an unmodified lithotriptor), 171 patients treated with ureteroscopy or spontaneous stone passage (control subjects), 25 patients who received PCNL only, and 34 patients treated with both ESWL and PCNL. In patients who received ESWL only, the annualized incidence of hypertension (2.4%) did not differ significantly from that in control patients (4.0%). Among patients who received ESWL, no correlation was found between the incidence of hypertension and unilateral vs bilateral treatments, the number of shock waves administered, the kilovoltage applied, or the power (number of shock waves times kilovoltage). However, there was a significant rise in diastolic blood pressure after treatment with ESWL (0.78 mm Hg), but not in the control group (−0.88 mm Hg). The long-term significance of this change in diastolic blood pressure following ESWL is unknown and requires further study (*JAMA*. 1990;263:1789-1794).

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Strictureplasty of the Small Bowel in Patients With Crohn's Disease

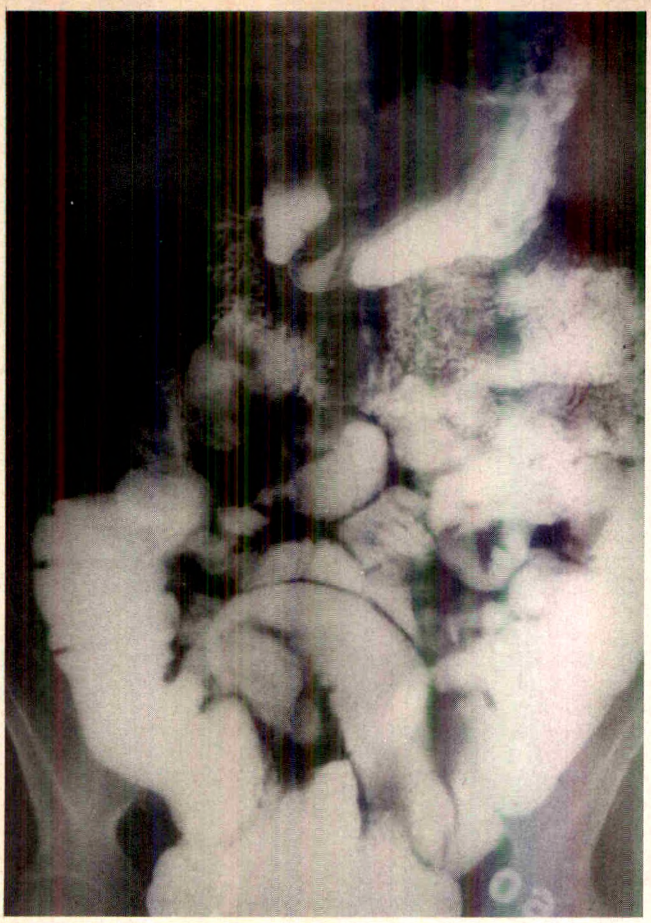
An Effective Surgical Option

Timothy J. Pritchard, MD; David J. Schoetz, Jr, MD; Fillor P. Caushaj, MD; Patricia L. Roberts, MD;
John J. Murray, MD; John A. Coller, MD; Malcolm C. Veidenheimer, MD

• Fibrotic strictures of the small bowel are known to cause chronic bowel obstruction in patients with Crohn's disease. Strictureplasty without resection permits relief of bowel obstruction and preservation of bowel length. The records of 13 patients who underwent 52 strictureplasties for Crohn's disease at the Lahey Clinic Medical Center, Burlington, Mass, from 1982 through 1989 were reviewed to determine the results of this surgical intervention. Nine patients were treated with strictureplasty only, while the remaining 4 patients underwent concomitant small-bowel resection for stenosed areas not amenable to strictureplasty. One early complication occurred in a patient in

[redacted]

reviewed to determine the immediate and long-term results of this surgical intervention. Eight men and 5 women (median age, 37 years; range, 22 to 54 years) constituted the study population. Median duration of Crohn's disease was 168 months (range, 21 to 384 months). At the time of initial strictureplasty, 10 patients had a history of 25 total previous hospital admissions for Crohn's disease, most commonly for medical treatment of small-bowel obstructive symptoms. Three patients had not required previous in-hospital care for Crohn's disease. Of the 13 patients, 7 had undergone previous small-bowel resections, 2 of which were extensive and resulted in short-bowel syndrome. Twelve patients were taking prednisone (dose range, 10 to



Follow-through examination of a patient with Crohn's disease of the small bowel and multiple enteric strictures.

Strictureplasties and Small-Bowel Resections Performed in Study Patients

Patient No.	No. of Strictureplasties (n=52)	Length of Small-Bowel Resection (Fixed), cm*
1	6	. . .
2	3	. . .
2†	1	. . .
3	4	45
4	5	45
5	1	22
6	2	. . .
7	4	. . .
7†	1	. . .
8	4	. . .
9	4	. . .
10	2	. . .
11	4	. . .
11†	1	24
12	9	. . .
13	1	. . .
13†	. . .	17

*Some resections included more than one stricture.
†Second operation.

(range, 1 to 9; Table). A longitudinal enterotomy was made through the stricture and was extended to include a 1.5- to 2.0-cm nonstrictured margin on either side. Transverse closure of the enterotomy completed the procedure. Fifty strictureplasties on short strictures were performed using the Heineke-Mikulicz technique, while 2 were constructed with a Finney type of configuration because of the length of the stricture. Of the 52 strictureplasties, 44 employed a two-layer closure technique using an inner layer of running sutures of chromic catgut and an outer serosal layer of sutures of braided nylon. The remaining 8 strictureplasties used a one-layer closure of running sutures of polyglactin.

Median hospital stay for patients undergoing strictureplasty was 13 days (range, 7 to 41 days). Patients were discharged on median postoperative day 10 (range, day 6 to 17). The immediate postoperative courses of all but two patients were without complications. In one patient, a mild gastritis developed that responded to antacid therapy. The only serious complication occurred in a 42-year-old patient with long-standing steroid-dependent Crohn's disease who was readmitted 2 weeks after discharge for operative drainage of a pelvic abscess. The abscess was thought to have been the result of leakage at the suture line from a two-layer Heineke-Mikulicz strictureplasty. After successful treatment of the abscess, the patient required admissions for progressive Crohn's disease, chronic small-bowel obstruction, and eventual strictureplasty of a newly stenosed area of small bowel 4 years after the original strictureplasty. No enterocutaneous fistulas occurred as a result of strictureplasty.

Median duration of follow-up in the 13 patients in this study was 2 years (range, 0.5 to 7 years). Nine patients were rehospitalized because of small-bowel Crohn's disease. These nine patients were initially treated medically for recurrent symptoms, but four of these nine patients required further operation. Three of these four patients had another strictureplasty performed in a newly stenosed area of small bowel 4, 5, and 6 years from the time of original strictureplasty. The fourth patient required resection of a previous strictureplasty. The remaining five patients have had recurrent symptoms of Crohn's disease consisting of abdominal pain, vomiting, diarrhea, gastrointestinal tract bleeding, or difficulty with maintenance of weight, and their disease has been managed pharmacologically.

Only four patients are asymptomatic after the original strictureplasty. Follow-up time in this subgroup averages only 1 year. Two of the three patients who required an additional strictureplasty are also asymptomatic after 1 year.

Two patients presented for their original strictureplasty with the diagnosis of short-bowel syndrome (one of these patients required home total parenteral nutrition). In no patient, however, did the short-bowel syndrome develop as a result of strictureplasty management in the study population.

COMMENT

The relapsing nature of Crohn's disease of the small bowel dictates that treatment strategies seek to preserve small-bowel length and minimize bothersome clinical symptoms of the disease. Most series[5,6] indicate bowel obstruction as the most common indication for surgery in patients with Crohn's enteritis. Recurrence of disease varies from 12% to 66% and frequently requires surgical intervention.[5,7]

From this review of an 8-year experience with 52 strictureplasties at the Lahey Clinic Medical Center, this procedure is an effective surgical option for patients with Crohn's disease who have symptomatic small-bowel strictures. Though most patients were not free of symptoms from Crohn's disease 1 year after operation, clinical and radiologic evidence of progression of disease in nonstrictureplastied areas of the small bowel appeared to be responsible for the majority of complaints. One pelvic abscess occurred after operation, and one strictureplasty failed in the 2-year median follow-up period. This latter problem occurred 18 months after the original procedure and was treated by limited small-bowel resection.

Strictureplasty—Pritchard et al

Options for treating obstruction secondary to small-bowel stricture in patients whose Crohn's disease failed to respond to medical therapy include small-bowel resection, balloon dilatation, intestinal bypass, and strictureplasty.[5,8,9] Definitive therapy with preservation of bowel length is best accomplished by strictureplasty, but this procedure is not without short-term and long-term complications. A single leak from 52 strictureplasty suture lines (rate, 2%) in this series is acceptable compared with one other study[10] that addressed complications of bowel anastomoses in patients with Crohn's disease. Although fistula formation is a well-recognized complication of small-bowel surgery in this patient population, no instances of this problem were observed.

Kendall and associates[2] described 9 patients with Crohn's disease who underwent 45 strictureplasties. Only 3 patients were free of symptoms with a follow-up interval of approximately 2 years. In another series, Silverman and associates[3] described 9 of 14 patients who were asymptomatic after multiple strictureplasties, but the duration of follow-up was only 16 months. In these series,[2,3] corticosteroids were a first-choice treatment option for patients with recurrent symptoms that followed strictureplasty. After an investigative workup, surgical intervention was undertaken only in the presence of obstructive disease refractory to pharmacologic manipula-

[redacted]

even short strictures (which are most amenable to this procedure) often do not consist merely of a fibrotic bowel wall with a healed mucosa, but frequently have associated mucosal inflammation and ulceration. Dr Pritchard and his colleagues have again documented the safety and efficacy of this operation. Fifty-two strictureplasties with one leak and one documented restenosis, which amounts to a 4% specific complication rate (2% of each type), is obviously not only acceptable but commendable. However, the longevity of freedom from symptoms was a bit disappointing, as it has been in other centers as well.

At the time of operation, it is often helpful to calibrate the intraluminal diameter of each of the frequently multiple strictures that may be present to determine which need fixing. I have used a Baker tube for this purpose, since the Foley catheter, which others have recommended, can prove to be too short. I would ask Dr Pritchard whether they routinely traverse the bowel in some such fashion. If not, is it possible that some of your apparently newly developed strictures requiring reoperation were, in fact, missed strictures? Also, could this factor have accounted for any of the recurrent symptoms in the five symptomatic patients who were not given reoperation?

I routinely mark each strictureplasty site with hemostatic clips. You indicate that you think that so marking the sites is a good idea, but you did not actually do that, as I understand it, in this particular series. Therefore, my second question is, in the patients with recurrent symptoms, but not given reoperation, how certain are you that their strictureplasty sites are not contributing to their problems?

Surgical Therapy for Recurrent Liver Metastases From Colorectal Cancer

Michael D. Stone, MD; Blake Cady, MD; Roger L. Jenkins, MD; William V. McDermott, MD; Glenn D. Steele, Jr, MD, PhD

• Forty percent of patients whose disease recurs after hepatic resection for liver metastases from colorectal cancer initially will have liver-only metastases. We have retrospectively reviewed our experience with repeated surgical treatment for liver-only recurrence after previous hepatic resection for colorectal metastases. Repeated hepatic procedures were performed with no mortality in 10 patients. Intraoperative ultrasound allowed identification of three unsuspected metastases and determination of unresectability of two metastases during 11 procedures. Three patients were free of disease at 31, 41, and 48 months from the first hepatic procedure and at 15, 31, and 43 months from the second procedure. Five patients have remained free of hepatic disease. Patients whose initial metastases were less than 6 cm in diameter and had single liver recurrences after hepatic resection appeared to be the best candidates for further surgical therapy. These data and a review of the literature suggest that surgical treatment of recurrent liver metastases from colorectal cancer can be performed safely, and it is associated with long-term disease-free survival in up to 38% of highly selected patients.

(*Arch Surg.* 1990;125:718-722)

Surgical resection of isolated hepatic colorectal metastases is now widely accepted as the only curative treatment modality available. Approximately 25% of patients with isolated hepatic metastases have tumors that are resectable, and 20% to 35% will survive 5 years or more.[1,2]

Nonetheless, 75% to 80% of patients who undergo hepatic resection for colorectal metastases will have disease recur in one or more sites. Initially, up to 40% of re-recurrences are found in the liver only.[3] While considerable interest has been focused on the identification of factors that predict recurrence,[2,4,5] little information is available regarding the outcome of further surgical treatment of patients with liver-only recurrence after hepatic resection.

In this article, we report our experience with repeated surgical treatment by resection and/or cryoablation for intrahepatic recurrence of colorectal metastases after previous hepatic resection.

MATERIALS AND METHODS

A retrospective chart review of 95 consecutive patients treated in our institution with hepatic resection for colorectal metastases between 1966 and 1988 has previously been reported.[5] Recurrent hepatic disease was found in 43 patients (45%), and in 27 patients (28% of the total, and 63% of those patients whose disease recurred in the liver), the liver was the only site. Of these 27 patients, 7 (7% of the total, 16% of those patients whose disease recurred in the liver, and 26% of those patients whose disease recurred in the liver only) underwent a second operation. Another 3 patients underwent their initial hepatic resection elsewhere and their second procedure at our institution, making a total of 10 patients included in this review.

Physician and hospital charts were reviewed and the following data were collected: age; primary site and stage (Astler-Coller modification of Duke's classification); carcinoembryonic antigen (CEA) level before resection of the primary or recurrent tumor; disease-free intervals; number, location, and size of hepatic metastases; procedures performed; margin of resection; other therapy; and survival time and status when last seen.

The median follow-up from the first hepatic resection was 33.5 months (range, 15 to 49 months), and from the second hepatic procedure, it was 13.5 months (range, 6 to 43 months). Disease-free intervals were calculated from the primary colorectal resection to the first liver recurrence, the first hepatic resection to re-recurrence, and the second hepatic procedure to recurrence or last follow-up.

The CEA levels before the initial hepatic resection and the second hepatic procedure were available for seven and eight patients, respectively. Metastatic disease was confirmed by findings from imaging studies or physical examination before reoperation in all cases. No operations were performed for an elevated CEA level alone.

Patients who underwent resection of all metastases or cryoablation of one or two hepatic nodules, as well as resection of all other disease, were considered to be free of disease. When cryotherapy was used, two freeze-thaw cycles were used for each lesion.[6] Cryoablation was considered to be satisfactory if, by intraoperative ultrasound (IOUS) monitoring, the "freezeball" completely encompassed the area of the lesion during both cycles.

If, at hepatic resection, tumor was grossly more than 1 cm from the cut surface of the unfixed liver specimen, the surgical margin was considered to be negative.[4,5] If tumor was found to be less than 1 cm away from the cut surface, the margin was considered to be positive. Involvement of Glisson's capsule was not considered to be a positive margin. Three patients received systemic therapy (fluorouracil (5FU)/platinum in one, fluorouracil/leucovorin calcium in another,

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Table 1.—Surgical Procedures in All Patients*

	1st Resection				2nd Procedure				Recurrence		Survival, mo		
Patient	DFI1	METS	Operation	MAR	DFI2	METS	Operation	MAR	DFI3	Site	OS1	OS2	Status
1	0	1	R lobe	NEG	17	1†	L wedge	POS	1	LU, H	49	25	DOD
2	13	1	R wedge	POS	9	1	R lobe	NEG	31	N	41	31	NED
3	15	5	R lobe, L CRYO	POS	5	3	L CRYO 2 lesions	POS	0	H, LU	43	34	AWD
4	64	1	R lobe	NEG	6	3	R wedge L CRYO	POS	5	H	17	9	AWD
5	27	3	R wedge, L CRYO 2 lesions	POS	0	1	R wedge	NEG	43	N	48	43	NED
6	17	2	R SEG, L LAT SEG, CRYO 2 lesions	NEG	13	2	R wedge	POS	5	LU	23	6	AWD
7	48	3	L lobe	POS	6	2	R wedge 2 lesions	NEG	6	P, H	35	29	DOD
8	12	1	L lobe, EXTEND	POS	20	1	R wedge	NEG	12	P, LU	32	12	DOD
9	24	1	R TRISEG	NEG	6	2	L wedge 2 lesions	NEG	9	H	15	9	DOD
10	6	3	R lobe	POS	7	1	L caudate	POS	15	N	31	15	NED

*DFI1 indicates disease-free interval after resection of primary; METS, number of metastases; MAR, margin; DFI2, disease-free interval after initial hepatic procedure; DFI3, disease-free interval after second hepatic procedure; OS1, overall survival from first resection; OS2, overall survival from second procedure; LOBE, lobectomy; NEG, negative (>1 cm); POS, positive (<1 cm); LU, lung; H, hepatic; DOD, dead of disease; N, none; NED, no evidence of disease; CRYO, cryoablation; AWD, alive with disease; SEG, segmentectomy; LAT, lateral; P, peritoneum; EXTEND, extended lobectomy; and TRISEG, trisegmentectomy.

†Many satellites.

and tumor necrosis factor in a third) for recurrence after the second hepatic procedure. All subsequently died of disease.

RESULTS

There were four males and six females. The median age was 54.5 years, ranging from 45 to 67 years. The location of the primary cancer was the sigmoid colon in four patients, the right colon in two, the left colon in two, the rectum in one, and not known in one patient whose colon resection was performed at another institution. The primary colon cancer stage was A in two patients, C1 in two, C2 in four, D (synchronous liver metastasis) in one, and unknown in one.

The initial hepatic surgical procedures (Table 1) included five anatomic lobectomies, one extended left-sided lobectomy, two wedge resections, a left lateral segmentectomy, and a right trisegmentectomy. Seven patients underwent resection only, and three patients were treated by cryoablation of one (patient 3) or two metastases (patients 5 and 6), in addition to resection.

The second hepatic surgeries (Table 1) included one lobectomy and eight wedge resections of one or two lesions. Patient 7 underwent resection of a local recurrence in association with a wedge resection of two hepatic lesions. Eight patients were treated by hepatic resection alone, one by cryoablation alone of two lesions (patient 3) and one by cryoablation in addition to a wedge resection (patient 4).

Among seven patients whose primary liver resection was performed at our institution, there were no deaths and one major complication (subphrenic abscess). There were no deaths and two complications (subphrenic abscess and hemorrhage) after the second hepatic surgery.

The IOUS was used during five of seven initial hepatic procedures. The IOUS identified two unsuspected metastases and an incidental renal cell carcinoma in patient 10 and unresectability of a lesion in proximity to the left hepatic vein in patient 3. The IOUS was used to guide and monitor cryoablation in patients 3, 5, and 6 and demonstrated unsatisfactory freezing of one lesion in patient 5.

Intraoperative ultrasound was used in 6 of 10 second hepatic procedures, and unsuspected lesions were identified in patients 3 and 4. In patient 3, an unsuspected lesion was demonstrated to be both unresectable and unsatisfactory for freezing because of proximity to an hepatic vein. The IOUS was used to guide cryoablation in patients 4 and 6, indicating unsatisfactory freezing in patient 4. In summary, the IOUS was used in 11 procedures and identified extra metastases in 3, determined unresectability of lesions in 2, and was used to guide cryoablation in 5.

Cryoablation was used to treat four metastatic lesions in three patients during the first hepatic procedure (Table 1). In patient 5, freezing of one of two cryoablated lesions was unsatisfactory. This metastasis was observed for 5 months. Wedge resection could then be performed with a negative margin in a regenerated liver. At the second hepatic procedure, three lesions in patients 3 and 4 were treated by cryoablation. In patient 3, two metastases were cryoablated, but a third was both unresectable and unsatisfactory for freezing because of location. In patient 4, freezing of an unresectable lesion was incomplete, and recurrence was noted at 5 months. At the second hepatic surgery, a biopsy specimen obtained under direct vision of two previously frozen lesions in patients 5 and 6 showed collapse of hepatic architecture with diffuse fibrosis, foreign-body granulomas, and no tumor.

At the first hepatic resection (Table 1), a negative surgical margin was achieved in four patients by means of formal lobectomy (two), trisegmentectomy (one), and wedge resection (one). A negative margin was achieved at the second hepatic procedure in five patients, four of whom had had a positive margin at the first resection. Six patients had a positive margin at the first hepatic resection. Five patients underwent complete resection at the second procedure, and four were rendered free of disease with negative margins.

The time to recurrence of disease diminished with each successive procedure. Median disease-free intervals were 17 months (range, 0 to 64 months) after primary colorectal resection (from the primary colorectal resection to the first liver recurrence), 7 months (range, 0 to 20 months) after the first hepatic procedure (from the first hepatic resection to re-

Table 2.—Size of Initial Metastases, Number of Recurrences, and Outcome*

Patient	Largest Metastasis†	No. of Recurrences‡	DFI3	Status
1	7	1§	1	DOD
2	4	1	31	NED
3	8	3	0	AWD
4	10	3	5	AWD
5	6	1	43	NED
6	6	2	5	AWD
7	11	2	6	DOD
8	15	1	12	DOD
9	14	3	9	DOD
10	3	1	15	NED

*DFI3 indicates disease-free interval after second hepatic procedure; DOD, dead of disease; NED, no evidence of disease; and AWD, alive with disease.

†Diameter in centimeters of largest metastases at first hepatic procedure.

‡Number of metastases at second hepatic procedure.

§Many satellites.

recurrence), and 6 months (range, 1 to 12 months) in those whose disease recurred after the second hepatic procedure (from the second hepatic procedure to recurrence). Patient 1 was considered not to be free of disease after primary resection (unresected synchronous metastasis), patient 5 was not free of disease after the first hepatic procedure (incomplete cryoablation of one lesion), and patient 3 was not free of disease after the repeated hepatic resection (one lesion unresectable and unfreezable).

Overall survival from first hepatic resection ranged from 15 to 49 months. Three patients (patients 2, 5, and 10) were free of disease at 31, 41, and 48 months, respectively. Measured from the second hepatic procedure, overall survival ranged from 6 to 43 months (Table 1). Two patients are alive with liver metastases at 9 and 34 months (patients 3 and 4, respectively), and one patient is alive with a lung metastasis at 6 months (patient 6). Four patients died of disease at 9, 12, 25, and 29 months. Eight patients were treated by resection of all metastatic disease at the second hepatic procedure. Three of these eight patients were free of disease at 15, 31, and 43 months, respectively, and two patients are alive, free of hepatic disease but with peritoneal and/or lung metastases at 6 and 12 months, respectively. All recurrences after the second procedure were noted within 12 months.

We had previously identified the following as significant predictors of recurrence after hepatic resection: a disease-free interval of less than 2 years, a CEA level greater than 200 ng/mL, more than two lesions, and surgical margins less than 1 cm.[5] These variables, as well as lobe involvement and tumor size, were determined for both hepatic procedures. All patients with any metastasis at the first hepatic resection larger than 6 cm in diameter have recurred again, regardless of the number of metastases or surgical margin at that procedure (Table 2). Three of four patients with a single metastasis at the second hepatic procedure have remained free of disease at 15, 31, and 43 months, respectively, from that procedure (patients 2, 5, and 10; Table 1). Patient 8 also had a single recurrent liver metastasis but had a 15-cm initial metastasis and died of disease.

COMMENT

Seventy-five to eighty percent of patients who undergo hepatic resection for isolated metastases from colorectal cancer will have disease recur again.[2] Several recent reports have attempted to identify prognosticators for recurrence.[2,4,5,7] The availability of such prognosticators would improve patient selection and outcome. Although the presence of extrahepatic disease or more than three metastases are strong predictors of recurrence, no single risk factor that precludes survival after hepatic resection of colorectal metastases has been identified.[2] Therefore, disease will recur in a substantial percentage of patients who undergo a hepatic resection. Approximately 45% to 50% of patients will have recurrences in the liver, and 28% will initially have liver-only metastases.[3] For the latter group of patients, as for those with an initial hepatic recurrence after resection of the colorectal primary, surgical resection remains the only potentially curative treatment modality.

Nonetheless, repeated resection was rare enough to be left unmentioned in two recent reviews of hepatic resection for colorectal metastases.[1,8] The low frequency of repeated resection for liver recurrence may be related to a paucity of suitable patients, reluctance to reoperate because of potential operative difficulty and morbidity, and skepticism regarding benefit.

Hepatic recurrence after liver resection is an uncommon indication for resection. Recurrence after hepatic resection may be limited initially to the liver in 40% of patients whose disease recurs, and subsequent extrahepatic metastasis reduces this figure to 22%.[2] In our series of 95 hepatic resections, 27 patients had subsequent liver-only recurrence, and only 7 (7%) underwent a second hepatic procedure. The frequency of second hepatic resections for recurrent hepatic colorectal metastases in other series was 8.5% and 10% of those initially resected.[9,10] These data indicate a substantial natural and surgical selection process. Comparison of survival data of patients who undergo repeated resection with those with liver-only recurrence who do not undergo a second procedure is therefore inappropriate, as the surgically treated group is a highly selected subset with more favorable disease.

The optimum patient selection criteria for repeated surgical therapy are not clear. Disease recurred after repeated therapy in all patients with initial metastases larger than 6 cm or with more than one recurrent liver metastasis after hepatic resection (Table 2). The importance of metastasis size is unclear, given the small number of patients and the lack of evidence that metastasis size is a survival discriminant in other series of initial hepatic resection for colorectal metastases.[2,5]

Although the report of Griffith and colleagues[10] of two patients with disease-free survival of 50 and 67 months after repeated resection of hepatic metastases suggests that multiple recurrent metastases after hepatic resection may not preclude long-term survival, the presence of more than three metastases is a predictor of recurrence after initial hepatic resection.[2] None of our patients with more than one hepatic recurrence after hepatic resection has remained free of disease. A thorough search for other metastases should be carried out before a second hepatic procedure in such patients. Since the lung and peritoneal cavity become more important sites of metastatic disease after hepatic resection,[2,11] evaluation before a second resection should include abdominal and chest computed tomographic (CT) scans, as well as a careful exploration of the abdominal cavity at the time of surgery.

The short disease-free interval of less than 12 months (Table 1) in all patients whose disease recurred again after second hepatic procedures indicates that these metastases were present at the time of the second hepatic procedure. It therefore is appropriate to delay second resections in all patients with more than one lesion, allowing time for other unsuspected metastases to become evident. In addition, we believe that IOUS should precede all liver resections for colorectal metastases. Our experience in finding additional lesions, determin-

Table 3.—Literature Survey*

Source, y	N	1st Procedure	2nd Procedure	Follow-up, mo
Nordlinger et al,[13] 1987	6	6 wedge	3 trisegmentectomy, 2 lobectomy, 1 wedge	2 NED (2, 12), 3 AWD (14, 16, 28), 1 DOD (10)
Butler et al,[14] 1986	2	2 wedge	2 lobectomy	2 NED (6, 17)
Griffith et al,[10] 1990	9	9 wedge	6 lobectomy, 2 wedge, 1 trisegmentectomy	7 NED (9, 19, 21, 25), (31, 50, 67), 1 AWD (16), 1 POD
Dagradi et al,[15] 1987	9	9 wedge	3 lobectomy, 5 wedge, 1 segmentectomy	5 ALIVE (1, 5, 14), (17, 20), 4 DOD (12, 18, 21, 37)
Fortner,[16] 1988	3	3 lobectomy	3 wedge	1 AWD (39), 1 DOD (16), 1 ALIVE (5)
Lange et al,[9] 1989	9	4 lobectomy, 1 lobectomy + wedge, 2 segmentectomy, 2 wedge	2 lobectomy, 1 lobectomy + segmentectomy, 1 lobectomy + wedge, 5 segmentectomy	4 NED (1, 3, 23, 24), 1 AWD (6), 4 DOD (6, 15, 24, 41)
Present series	10	6 lobectomy, 1 trisegmentectomy, 2 wedge, 1 segmentectomy	1 lobectomy, 8 wedge, 1 cryoablation only	3 NED (15, 31, 43), 3 AWD (6, 9, 34), 4 DOD (9, 12, 25, 29)

*NED indicates no evidence of disease; AWD, alive with disease; DOD, dead of disease; POD, postoperative death; ALIVE, not otherwise specified.

ing resectability of known lesions, and identifying anatomic landmarks is consistent with the report of Parker et al[12] that the IOUS results in a change of the surgical plan in up to 40% of cases.

A second hepatic resection is safe and well tolerated as shown by the absence of mortality and 20% morbidity in the present series. Patients with initial surgical margins less than 1 cm, which is associated with a significant survival disadvantage,[2,4] may be rendered free of disease with clear margins by repeated resection. Although 3 of our 10 patients have remained free of disease from 15 to 43 months after a second resection, suggesting a benefit from resection, the duration of follow-up is relatively short. We therefore have reviewed the literature for other reports of second resections of hepatic metastases from colorectal cancer.

Six other reports have described patients who were treated by repeated hepatic resection for colorectal metastases (Table 3).[9,10,13-16] Among 48 patients (including the present series) who underwent second hepatic procedures, there was one operative death. Eighteen (38%) of 48 patients have been free of disease at a median of 19 months (range, 1 to 67 months) after the second resection. Another 6 patients (12%) are alive (not otherwise specified), and 10 patients (21%) are alive with disease at a median of 9 months (range, 1 to 20 months) and 16 months (range, 6 to 39 months), respectively from the second resection. Only 29% are known to be dead of disease.

These data indicate that a second hepatic resection is feasible and safe and may be associated with long-term survival in highly selected patients. We believe that repeated resection should be limited to patients with single hepatic recurrences after hepatic resection. All candidates for a second surgical procedure should be carefully examined preoperatively by chest and abdominal CT scans for extrahepatic disease. At all operations for hepatic colorectal metastases, the peritoneal cavity should be carefully explored for extrahepatic disease, and IOUS should be performed before resection to identify unsuspected hepatic lesions. Conservative resection of hepatic parenchyma, as has been advocated by Lange et al,[9] is appropriate provided that a 1-cm margin is achievable.[2,4]

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Discussion

Randolph B. Reinhold, MD, Boston Mass: I would like to ask the authors if they would comment a little further about the cryoablation question. We tried it several years ago in a few patients and found that, in fact, disease recurred within a period of a few months. If I read the abstract correctly, it would appear that disease recurred in the patients, at least for the re-resection, who were ablated, and the patients were either alive or dead with recurrent disease. I wonder if it is currently really as effective as we thought it might have been for the control of hepatic metastases.

C. Elton Cahow, MD, New Haven, Conn: The place of hepatic resection in the treatment of metastatic carcinoma has been well documented in the literature during the past 20 years. One of the earliest and most convincing of these reports was the monograph written by the president of this organization, Dr James Foster. It was his publication that, for the first time, correlated the large experience in this field into one volume. It was also that publication, I think, that gave many of us the courage to go ahead at a time when those around us were nay-sayers. Subsequently, Dr Martin Adson eloquently summarized his vast experience in hepatic resection for metastatic carcinoma in the Second Annual Samuel Jason Mixter Lecture before the New England Surgical Society in 1986. There is now little question about the efficacy of hepatic resection for metastatic carcinoma.

We have been privileged to hear the next step in this process—the surgical treatment of recurrent, or most probably persistent, metastatic carcinoma of the liver. Dr Stone and his coauthors have presented 10 patients who underwent repeated surgical treatment of their disease. The results are impressive and should give us all cause for thought and hope for better results. However, this is a new step, or an extension of what has gone before, and we must ask the authors and ourselves several questions. As has been so eloquently asked, "When is enough enough?" Can we expect the same recurrence rate after the second resection, ie, the 75% to 80% recurrence rate after the first resection? Will this be true after the second resection? Then, do we do third or fourth or fifth resections? When do we stop?

Second, should patients who have their first resection for hepatic metastases receive adjuvant therapy, most likely chemotherapy? Would this have prevented these recurrences and prevented further surgery?

Third, how do you follow up these patients after hepatic resection for metastases? Is a simple CEA level determination enough, or do they have to undergo magnetic resonance imaging scans, CT scans, or ultrasound examinations every 6 months?

In your manuscript, you underlined "satisfactory cryoablation" as a curative procedure. How do you define satisfactory cryoablation, and how do you determine that at the time?

Finally, what is the place of ultrasound during the first operation? Should this be carried out on all patients? Could you have picked up some of these lesions at the time of the first resection and not have required a second resection?

I think this study ushers in the next stage of this therapy.

Claude H. Organ, MD, Oakland, Calif: I commend Dr Stone and his associates for bringing to our attention one of the extended parameters of surgery. We have sold ourselves short in the area of palliative surgery. Debulking procedures (which I presume are called *cytoreductive surgery* in New England) are important. Historically, the procedures recommended here will be another modality in our armamentarium to treat people with metastatic disease rather than giving them a bottle of narcotics and sending them home. We have demonstrated that hepatic surgery is safe today. Whether it is curative or designed to extend the quality of life will have to be defined in time. If CEA level determinations were unavailable in my hospital, it would be no great loss! It is expensive ($61), and although it has great specificity for recurrence, it has a low predictability for resectability.

Finally, every diagnostic modality that comes on the horizon is heralded as a great success until we find out the truth about it, and that has been true with CT scanning and staging. I have found, in assessing these patients for surgical debulking and staging procedures, that CT scanning is fraught with misinterpretation.

William F. Collins, Jr, MD, New Haven, Conn: As a specialty surgeon, I wonder if the authors would tell me what the indications are for determining that they have a recurrence. I did not hear that in the presentation, but I am sure they must have defined it. Is it a CT finding? Is it a physical finding?

Dr Stone: The first question of "When is enough enough?" is always a difficult one. Third and fourth resections have been performed in a number of institutions. In fact, some of those patients are alive and free of disease and included in the literature survey. When one should continue to resect liver metastases is not clear, but if you go back to the principles of metastasectomy at any site, those are fairly clear. One is that you have a tumor that is likely to metastasize to one site and one site only. This is true with sarcoma of the lung and, to some extent, is true of colon cancer in the liver. The patient needs to be medically fit for surgery; there needs to be no other disease; and the primary has to be controlled. The most important aspect is that there be no other effective therapy. Unfortunately, we continue to have no other effective therapy for colorectal cancer, so I think that as long as those other criteria are met and the patients are carefully examined, then it is not unreasonable to continue.

As far as adjuvant therapy is concerned, none of these patients received adjuvant therapy. Three of them were treated with systemic therapy after their third recurrence. As long as the response rates of adjuvant therapy are in the 20% to 30% range, we are not likely to alter the median survival of these patients. Therefore, I do not see any indication for it at the present time.

As far as the follow-up of these patients is concerned, there was no specified follow-up in our institution. The CEA levels were measured in a number of patients, but no patient underwent surgery on the basis of an elevated CEA level. All had diagnostic imaging tests, usually CT scans, which demonstrated lesions.

In terms of how one should follow up these patients, one should look only for those things that one can do something about. At the present time, we can do something about liver metastases in a number of patients. Therefore, a CT scan of the abdomen every 6 months may be appropriate, as well as a chest x-ray film. There are a number of reports of long-term survival after pulmonary resection for isolated colorectal metastases.

Several discussants asked what constitutes satisfactory cryoablation. In our institution, that is defined as two 8-minute freeze-thaw cycles, with ultrasound guidance demonstrating that the freezeball completely encompasses the lesion during both cycles. We had a number of technical problems in these patients because of the location of the tumors. In one patient, the cryotherapy machine essentially broke down. In another patient, the tumor was close to one of the hepatic veins, and during the freeze cycle, that tumor was warmed by the blood in the vein and was not completely frozen.

The long-term results of cryoablation are not entirely clear. Dr Ravikumar presented the data from the New England Deaconess Hospital, Boston, Mass, a few years ago. He is currently updating that information. At the present time, what we can say is that experimentally and clinically, it appears that 80% to 90% of lesions can be completely frozen and eradicated. Two patients who had cryoablation during the first procedure had biopsy specimens obtained under direct vision of the frozen lesions at the second procedure. Both of these biopsy specimens showed liver necrosis, loss of architecture, and no tumor.

As far as IOUS at the first resection is concerned, I believe it should be part of the routine evaluation of hepatic metastases so that we can identify more lesions at that time. In addition to preventing second operations, it may, in fact, help us to understand which patients really are curable at the first resection.

Clinical and Pathologic Correlations in Patients With Periampullary Tumors

F. Maureen Martin, MD; Ricardo L. Rossi, MD; Vittorio Dorrucci, MD; Mark L. Silverman, MD; John W. Braasch, MD

• Perioperative data on 87 patients undergoing pancreatoduodenectomy for periampullary tumors were correlated with pathologic study of operative specimens to identify the accuracy of diagnosis and the factors affecting survival. Accuracy of endoscopic retrograde cholangiopancreatography and computed tomography in locating lesions was 75% and 44%, respectively. Histologic diagnosis before or at the time of resection was available in only 61% of the patients. Carcinoma was correctly diagnosed clinically by the pathologist or the surgeon in 95% (83/87) of patients with 4 patients found to have benign disease on final pathologic examination. Intraoperative diagnosis of site of origin was incorrect in 18% (16/87) of patients. In 28% (23/83) of patients, pathologists identified nodal metastatic disease missed by the surgeon. Survival correlated with nodal and margin status and tumor grade. Tumor size demonstrated no predictive capacity. Although preoperative diagnostic accuracy is less than optimal, surgeons can usually diagnose malignant lesions but more often fail to identify tumor origin and nodal disease. We continue to advocate resection for patients with periampullary lesions thought to be malignant and resectable without a positive histologic diagnosis.

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Periampullary tumors comprise a heterogeneous group of lesions having similar modes of presentation but associated with vastly different overall prognoses. Surgical management is sometimes dictated by the site of origin of the tumor, and more aggressive indications for resection are used

[redacted]

men and 38 women with a median age of 64 years (range, 19 to 82 years) formed the study population. Total pancreatectomy was performed in 11 patients, while the remaining 76 underwent pylorus-preserving proximal pancreatoduodenectomy. Three perioperative deaths resulted in a mortality rate of 3.4%. Results of preoperative CT and endoscopic retrograde cholangiopancreatography (ERCP) were reviewed with attention given to the site of the lesion and the presence and level of biliary or pancreatic ductal dilatation or obstruction. The method of obtaining a positive diagnosis before resection was documented. Operative reports were scrutinized for the surgeon's impression of the site and size of the lesion, the presence of nodal disease, and whether the resected margins were free of tumor. These findings were compared with the pathologic interpretation of the resected specimen, permitting documentation of the accuracy of findings before and during operation. Complete follow-up studies were obtained in all patients, through direct contact, hospital notes, or death certificates.

Analysis of survival distribution was carried out by the Kaplan-Meier product-limit method on patient groups presenting with ampullary adenocarcinoma (23 patients), adenocarcinoma of the pancreas (22 patients), bile duct adenocarcinoma (18 patients), and duodenal adenocarcinoma (8 patients). Five patients with islet cell tumor, 7 patients with pancreatic cystadenocarcinoma, and 4 other patients who ultimately proved to have benign disease (2 with chronic pancreatitis, 1 with ampullary adenoma, and 1 with sclerosing cholangitis) were excluded. These data were analyzed using the Cox proportional hazard model to determine the prognostic importance of various independent variables. Analysis was performed on an IBM PS/2-50 could not be distinguished. A double duct sign was seen in 8 patients and was considered pathognomonic of pancreatic carcinoma; however, 3 patients had distal bile duct lesions. Pancreatic lesions were found in 2 patients with normal results on ERCP. One patient had adenocarcinoma and 1 had cystadenocarcinoma. Overall ERCP accuracy was 74% (35/47). Surprisingly, 4 ampullary lesions were missed. Of 34 patients who underwent both CT and ERCP, 10 and 28 correct preoperative diagnoses, respectively, were obtained. Six patients with normal results on CT also underwent ERCP, with 5 correctly diagnosed as having ampullary (4 patients) or duodenal (1 patient) lesions. Endoscopic retrograde cholangiopancreatography appeared more sensitive (82%) than CT (29%) in these 34 patients.

Final pathologic diagnoses were as follows:

Diagnosis	**No. of Patients**
Pancreatic lesion	34
Ductal adenocarcinoma	22
Islet cell tumor	5
Cystadenocarcinoma	7
Ampullary lesion	24
Adenocarcinoma	23
Villous adenoma	1
Tumor of distal bile duct	18
Duodenal adenocarcinoma	8
Chronic pancreatitis	2
Sclerosing cholangitis	1
Total	87

Preoperative histologic diagnosis was obtained endoscopically in 15 patients and percutaneously in 1 patient, while intraoperative confirmation was obtained in 35 patients. Thirty-six patients (41%) underwent resection based solely on the surgeon's impression that the lesion was malignant. Four of 36 patients proved to have benign disease (chronic pancreatitis in 2 patients, ampullary villous adenoma in 1 patient, and sclerosing cholangitis in 1 patient). When pathologic data were compared with the preoperative and operative diagnoses in the group of 87 patients, agreement regarding a malignant lesion was present in 83 patients (95%).

Thirteen errors (25%) were noted regarding the surgeon's impression of the actual location of the tumor in 51 patients with preresection histologic features. Distal bile duct (in 7 patients) and ampullary (in 3 patients) lesions were most often interpreted as pancreatic adenocarcinoma. Two pancreatic adenocarcinomas and one pancreatic cystadenocarcinoma were thought to be distal bile duct (in 2 patients) or ampullary (in 1 patient) tumors.

The pathologist confirmed nodal metastatic disease in 29 patients (33%) of whom only 8 were believed by the surgeon to have metastatic disease. Vascular or portal vein invasion and positive margins were noted in 6, 5, and 11 patients, respectively. Tumor differentiation was graded as well (19 patients), moderate (24 patients), and poor (27 patients), with 7 miscellaneous and 7 not mentioned.

Two of three deaths were the result of multisystem organ failure with no evidence of leakage or abscess at autopsy in either patient. Autopsy confirmed that the third death was caused by a massive pulmonary embolus on the seventh postoperative day.

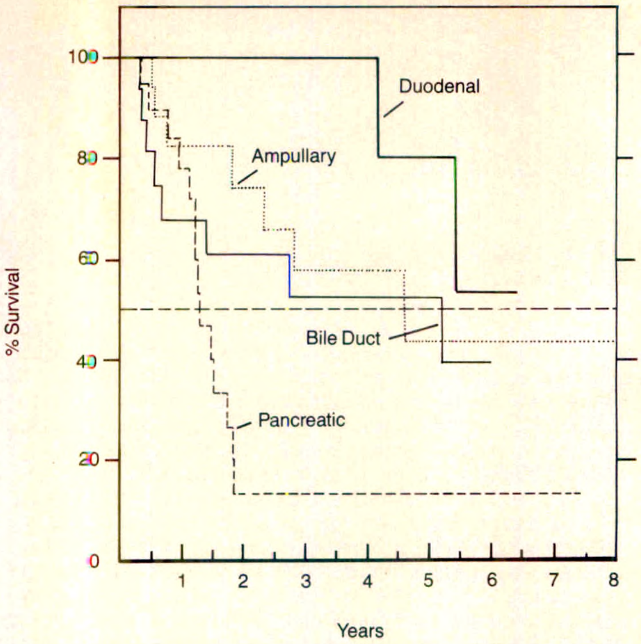

Fig 1.—Adjusted survival of all patients according to site of tumor.

Adjusted median survival times were 1.3, 4.6, 5.2, and 6.5 years for pancreatic, ampullary, bile duct, and duodenal adenocarcinoma, respectively. Five-year survival was 43.2%, 39.1%, and 53.3% for ampullary, bile duct, and duodenal adenocarcinoma, while 2-year survival for patients with pancreatic adenocarcinoma was 13.3% (Fig 1). Significant survival advantage was seen in patients with well-differentiated or moderately differentiated tumors when compared with patients with poorly differentiated tumors: 5-year survival rates of 65.8% and 61.4%, respectively, compared with 16.6% of patients with poor grades of tumors ($P = .01$). Similarly, 5-year survival with negative nodes was 60.9% compared with 9.7% when nodes were positive ($P = .01$). Of 11 patients with a positive margin, only 1 patient had a 5-year survival. No significant survival difference was noted when size of tumor was considered. Five-year survivals of 53.7%, 37.2%, and 43.6% resulted for patients with tumors less than 2, 2.1 to 3.9, and greater than 4 cm, respectively (Fig 2). Multivariate analysis demonstrated that disease found at margins of resection was the predictive variable with the highest hazard ratio (Table). The risk of death for a patient with positive margins is 4.99 times that of patients with negative margins. Similarly, patients with positive nodes had a risk of death 3.32 times that of patients with negative nodes, while poor tumor grade was associated with a risk of death 2.2 times that of patients with well-differentiated or moderately differentiated tumors. Figure 3 represents survival curves predicted for worst case (positive margin, positive nodes, and poor grade of tumor) and for best case (negative margin, negative nodes, and good to moderate grade of tumor).

When these variables were stratified by primary tumor site, nodal status had a major influence on survival. Stratification of other variables (tumor size, grade) resulted in sample sizes too small to permit computation. The 5-year survival rate (±SE) for patients with bile duct tumors without nodal involvement was 67.7% ± 13.4%, and no patients with positive nodes survived 5 years. The 5-year survival rate for patients with ampullary carcinomas and negative nodes was 66.7% ± 20.8%, with no 5-year survivors in the node-positive group because of early censoring. Patients with node-negative pancreatic carcinomas had a 5-year survival rate of 28.6% ± 17.1% with no 5-year survivors in the node-positive group. Difference based on nodal status was statistically significant at the $P < .05$ level for bile duct tumors and ampullary tumors. The pancreatic tumor groups were not significantly different at the $P < .05$ level (Tarone-Ware,[2] $P = .79$).

COMMENT

The preoperative diagnosis of the site of origin of periampullary lesions continues to challenge the surgeon and radiolo-

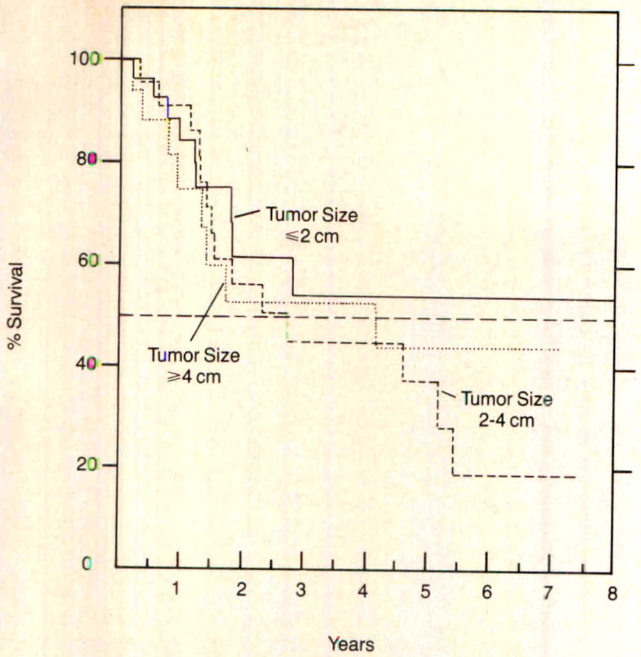

Fig 2.—Survival compared with size of tumor.

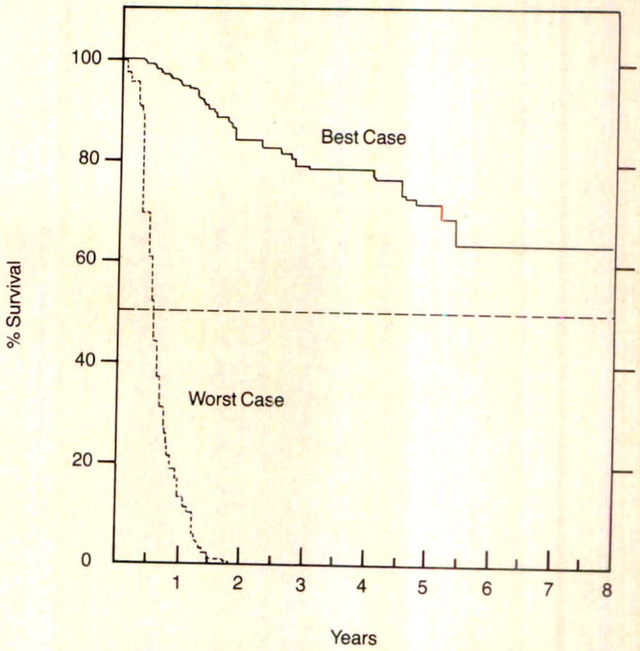

Fig 3.—Multivariate analysis of the worst case (positive nodes, positive margins, and poorly differentiated tumor) compared with the best case (negative nodes, negative margins, and well-to-moderately differentiated tumor).

Multivariate Analysis Using Cox Proportional Hazard Model*

Variable	Coefficient	SE	Hazard Ratio
Margin (positive)	1.6072	0.4720	4.9890
Node (positive)	1.2000	0.4529	3.3202
Grade (undifferentiated)	0.7957	0.4221	2.2159

*Log likelihood was equal to −95.2739. Independent variables included tumor margins, size, grade, nodal status, and presence of vascular invasion.

gist. Reluctance to perform radical resections for patients with periampullary lesions results from the dismal survival reported[3-5] for carcinoma of the head of the pancreas. Several studies[6-8] have documented improved results with pancreatoduodenectomy and noted that, in experienced hands, this procedure is warranted in patients in the good-risk category. The reliance on CT and ERCP to stage and confirm the origin of these lesions leaves some patients with ampullary or distal bile duct lesions without benefit of resection and improved survival. Computed tomographic assessment of periampullary lesions is poor in patients without dilated ducts or a mass in the head of the pancreas. The efficacy of CT staging to define lesions amenable to curative vs palliative surgical treatment has not been proved and, in fact, in the absence of obvious metastatic disease, cannot be recommended as a sole modality in determining resectability and ultimate treatment.[9] Our experience suggests that both CT and ERCP be utilized and considered complementary in the workup of patients with obstructive jaundice. More often than not, ERCP will accurately diagnose most lesions of the ampulla and pancreas and, when used with CT, will allow assessment of extrapancreatic spread. Difficulty arises when distinguishing ampullary tumors from distal bile duct tumors.

Diagnosis on the basis of percutaneous CT-guided histologic data has an accuracy of 50% to 90% but requires skilled cytologists, radiologists, and, at times, multiple passes to obtain adequate cells.[10,11] These facts raise concern regarding seeding of the tracts with tumor cells and the small but real risk of disseminating tumor cells intra-abdominally.[12,13] Even the surgeon at the operating table may be left with an equivocal pathologic diagnosis despite numerous needle aspirations and direct biopsies. We have abandoned percutaneous needle biopsy of the head of the pancreas in good-risk patients who appear to have resectable disease because the results will not affect our ultimate decision to perform exploratory operation. In our series, 59% of patients had a secure diagnosis before resection. The decision to perform resection in the remaining patients was left to the judgment of the surgeon. This decision proved to be highly sensitive when distinguishing malignant from benign disease. Two of four patients with benign lesions that were thought to be malignant would have undergone less radical procedures had a secure preoperative diagnosis been obtained. Although the decision would be controversial, one patient with a villous adenoma of the ampulla could have undergone local resection.[14] This patient subsequently died on the seventh postoperative day of a pulmonary embolus. The 71-year-old patient with sclerosing cholangitis could have undergone biliary diversion; however, to obtain proof of benignity from histologic data would have been difficult without resection. Both patients with chronic pancreatitis had lateralization of disease to the head of the pancreas, and pancreatoduodenectomy was an appropriate procedural choice.

The surgeon had some difficulty assessing nodal metastatic disease, and, as shown in the survival curves, this factor was a significant predictor of survival. Therefore, nodal sampling before resection is indicated. In patients with positive findings on biopsy obtained before resection, errors in determining the site of origin of the tumors were noted in 26%; however, the majority of these errors were in differentiating distal bile duct and ampullary tumors, each location associated with a relatively good prognosis. Improved survival correlated best with tumor site, negative nodes, negative margins, and moderate or well-differentiated tumors. Tumor size was a poor predictor of survival.

The low overall survival rates were not unexpected with pancreatic carcinoma, but survival rates of patients with ampullary, distal bile duct, and duodenal carcinoma were satisfactory. The poor correlation between the size of the tumor and patient survival further supports the need to deemphasize the use of nonoperative staging with CT alone. In the large majority of patients, the surgeon can accurately diagnose a malignant lesion. In the absence of obvious metastatic disease or advanced local spread of tumor, patients at good risk should have the benefit of surgical exploration and assessment of resectability firsthand. Even in the absence of a diagnosis based on histologic data, when the history and findings at exploration are typical of a malignant tumor, resection should be performed by the experienced surgeon, with only a small chance of its being inappropriate. Alternatively, in the patient at poor risk, nonoperative attempts at staging and histologic diagnosis using percutaneous techniques should be considered initially.

We thank Gerald J. Heatley, MS, of the Sias Surgical Research Unit of the Lahey Clinic Medical Center, for statistical assistance in the preparation of this report.

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Discussion

JAMES H. FOSTER, MD, Farmington, Conn: I was surprised to be asked to discuss this study because I suspect there are few in this room who are more negative about major pancreatic resection for ductal cancer of the pancreas than I. However, if these conclusions can be confirmed by others, this study may change my approach to periampullary cancer. I had not realized how bad our preoperative and intraoperative diagnostic skills were in differentiating the exact origin of local cancers.

If I've interpreted the numbers correctly, the CT scan alone was wrong about tumor origin in 44% of the patients; ERCP alone was wrong in almost 30% of the patients, even missing 4 ampullary cancers; and the surgeon at laparotomy was wrong about tumor origin in about one fourth of the patients, about nodes in a large majority of those eventually proven to be positive, and about margins in 11 of 37 patients. Computed tomographic scan, ERCP, and the surgeon were wrong in both directions.

I still believe that ductal cancer of the pancreas should seldom be resected. But if modern imaging and skilled surgeons cannot rule out curable cancer of the periampullary region in many patients, it seems to me we ought to waste less time in preoperative testing and ought to consider resection more often if lymph nodes are clinically negative and clear margins are possible. The differentiation between duodenal, bile duct, or ampullary origin becomes of academic interest only.

I do have one question, Dr Martin. Although the numbers were small, six of six of your patients who had CT scan evidence of a pancreatic mass and dilated ducts proved to have pancreatic ductal cancer. Is that combination enough to keep you out of the operating room in 1989?

ANDREW L. WARSHAW, MD, Boston, Mass: I find myself in the unusual position of having to take issue with the prior discussant more than with the presenter. There are a few issues that I would like to highlight. First, Dr Foster has said that if we could be sure that a given case was a pancreatic cancer, we should not be resecting because we so seldom cure these patients. The Lahey experience that we've just seen is really consistent with the national experience, in that about 13% of patients are cured. That's not insignificant, when the mortality of this operation has dipped below 5%.[6-8] The cost is worth the benefit. In addition, the author's main point is that we are often wrong about the origin of the tumor and that many will turn out to be not of pancreatic origin, and thus more likely to be cured.

Second, as has not been stated, even if the patient does not ultimately wind up in the "cure" column, the median survival after a Whipple operation is about 20 months. The median survival of a similar tumor only bypassed is about 6 months. I submit that the trade-off again is good.

Another point that has not been properly addressed in the presentation was the use of the word *staging*. Staging is not what this study was about; it was about diagnosis of the tissue of origin. Staging pertains to whether the tumor is resectable. How often will the patient who walks into our office have a tumor that is resectable from the point of view of metastatic disease or local involvement of the major mesenteric and other vessels? We have just presented our experience with the preoperative staging of 88 patients at the Society for Surgical Oncology.[15] Our conclusion is that with modern techniques, which to us means good angiography, good CT with contrast, and laparoscopy (which picks up the 27% of patients who have small metastases in the liver not seen by scanning techniques), we can identify 90% of the unresectable tumors and 80% of the resectable tumors in advance. Therefore, we can in most patients make the judgment that Dr Foster would like to make: pick the patients who are resectable vs those who are not.

I believe the Lahey Clinic group has in the past espoused the approach that one should determine resectability at the time of the operation. I would like to ask whether the authors are still taking this view.

DR MARTIN: The thing that I learned during my time at the Lahey Clinic was that we always had a rather thoughtful approach, and we are not at all hesitant to look at various radiologic approaches to helping us make the diagnoses. But the most important thing I learned at the Lahey Clinic was that very often the surgeon in the operating room was the person who had the final say in terms of what happened and what the status of the patient was and that we were very often walked down the garden path by the radiologists in a number of settings. I still think that holds today, so I'm going to attempt to answer Dr Warshaw's question before Dr Foster's questions.

I feel very strongly that surgeons do have a final word with these patients, and that one can do angiography, CT scanning, and ERCP and still have some idea as to what is going on, perhaps a more educated guess at what's going on. In that good-risk, well patient presenting with obstructive jaundice, I am not very sure that I could safely tell him that there was absolutely nothing I could do for him. So, I feel strongly about that approach.

Should we resect patients with cancer of the pancreas? I think that we should, and I think that in a patient who, once again, is a good risk with no evidence of gross metastatic disease and who at the time of surgery has a fairly well-contained tumor and negative nodes found on node sampling, we should go ahead and resect and allow him that additional 20-month survival that Dr Warshaw mentioned.

Resection of Cavoatrial Renal Cell Carcinoma Employing Total Circulatory Arrest

David M. Shahian, MD; John A. Libertino, MD; Leonard N. Zinman, MD; Howard K. Leonardi, MD; Robert C. Eyre, MD

• Intracaval extension of renal cell carcinoma to the right atrium is a life-threatening presentation that may result in fatal tricuspid valve obstruction or pulmonary embolization. From 1981 to 1989 we treated 10 patients with such extension of tumor, the last 7 of whom underwent resection in which hypothermic circulatory arrest was used. No postoperative deaths, myocardial infarctions, or strokes occurred. Four patients were alive with no evidence of disease at 4, 10, 16, and 39 months after resection, and 1 patient was alive with pulmonary and spine metastases at 34 months after resection. Two patients died of metastatic disease at 7 and 12 months. In the absence of diffuse metastatic disease, lymph-node involvement, or invasion of contiguous organs, radical resection of cavoatrial hypernephroma may result in excellent palliation and possibly a cure.

(*Arch Surg.* 1990;125:727-732)

Tumors of the kidney that extend through the inferior vena cava (IVC) to the right atrium present a formidable surgical challenge. With a properly planned operative approach involving both urologic and cardiovascular surgeons, however, resection of such tumors can be achieved with low mortality and morbidity, excellent palliation, and the potential for prolonged survival.

PATIENTS AND METHODS

From 1981 to 1989 we treated 10 patients with intracaval extension of a renal cell carcinoma to the right atrium. Seven of these patients underwent one-stage radical resection in which deep hypothermia and total circulatory arrest were used. The 3 men and 4 women, with a median age of 62 years, formed the basis of this report. Four of the tumors were on the left side and three on the right.

Presenting symptoms are listed in Table 1. None of the patients had symptoms or signs suggesting IVC obstruction. Despite extensive preoperative evaluation (Table 2) only one patient had evidence of distant metastatic disease—a single nodule in the right lung. Inferior venacavography was performed in all patients and suggested intra-atrial extension of the tumor. This was confirmed by superior venacavography in five patients (Figure) and two-dimensional echocardiography of the heart in six patients. Five patients underwent preoperative coronary angiography; two patients had significant coronary artery disease.

SURGICAL TECHNIQUE

In each of these seven patients tumor resection was performed with the aid of total circulatory arrest using our previously described technique.[1] The patient is positioned supine on the operating table with a thermostatically controlled warming blanket, electrodes for intraoperative electroencephalography, and rectal and nasopharyngeal temperature probes. An introducer and short central venous pressure catheter may be inserted, but they should terminate in the superior vena cava (SVC) to avoid embolization of friable intra-atrial tumor.

An initial bilateral subcostal or midline incision is made, and the abdomen is explored to assess resectability of tumor. The presence of liver metastases, nodal involvement, or invasion into the posterior musculature or mesocolon is a relative contraindication to further radical operative treatment. In the absence of these findings, sternotomy is performed, and the diaphragmatic surface of the pericardium is divided down to the IVC. A Langenbuch maneuver is performed in which the ligamentous attachments of the liver are mobilized, permitting its displacement to the left and cephalad. Dissection of the tumor and the IVC is performed with care to avoid tumor embolization.

When the tumor has been mobilized with the exception of its renal vein and IVC extension, heparin is administered and an ascending aortic perfusion cannula inserted. If extension of the tumor into the right atrium is limited, a 32F to 34F catheter can be inserted into the SVC through a purse-string suture in the cephalad aspect of the right atrium. If most of the right atrium is occupied by tumor, direct cannulation of the SVC through a purse-string suture on its anterolateral aspect is a safer procedure. Although a second venous drainage catheter can be inserted into the common femoral vein, we have recently begun to use only a single SVC cannula, relying on the presence of well-formed venous collaterals from the caudad portion of the body around the obstructed IVC.

Bypass is begun and the body temperature lowered at a rate not exceeding 1°C per minute. Methylprednisolone sodium succinate (Solu-Medrol, Upjohn, Kalamazoo, Mich), thiopental sodium (8 to 60 mg/kg), and mannitol are administered systemically for protection of the brain and vital organs during circulatory arrest. If distention of the heart occurs during cooling, a vent can be placed through the pulmonary artery or the right superior pulmonary vein. When the body temperature is lowered to 29°C to 30°C, the aorta is cross clamped and cold blood cardioplegic solution instilled into the aortic root until total electromechanical arrest and a septal temperature of 12°C are achieved.

The patient's head is encased in ice bags. When the rectal and nasopharyngeal temperatures have been lowered to 16°C to 18°C and

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Table 1.—Patient Demographics

Patient/ Age, y/Sex	Symptoms	Duration of Symptoms, mo	Tumor Side	Results of Preoperative Liver Function Tests*
1/52/F	Fatigue, weight loss, anemia, night sweats	8	L	Increase in alkaline phosphatase level
2/63/M†	Fatigue, flank mass, dyspnea, anorexia	1	R	Increase in alkaline phosphatase level
3/62/F	Flank pain, weight loss, chills	3	L	Increase in alkaline phosphatase level
4/59/F	Anemia, hematuria	1	R	Increases in alkaline phosphatase and LDH levels
5/69/F	Weight loss, anemia, dyspnea, chest pain, fatigue, night sweats	3	L	Increase in alkaline phosphatase level
6/69/M	Hematuria, pulmonary embolism	2	L	Normal
7/59/M	Flank pain, anorexia, dyspnea, weight loss, fatigue	4	R	Increase in alkaline phosphatase, AST, and bilirubin levels, and increase in PT

*LDH indicates lactate dehydrogenase; AST, aspartate aminotransferase; and PT, prothrombin time.

†Only patient 2 had a preoperative metastasis—a lung nodule.

Table 2.—Preoperative Evaluation

Test*	No. of Patients Who Underwent Test	No. of Patients With Abnormal Test Result	Findings†
Abdominal CT	7	7	Tumor + IVC extension
MRI	2	2	Tumor + IVC extension
Chest CT/tomography	7	1	RUL nodule
Liver scan/ultrasonography	4	0	. . .
Liver function	7	6	Increase in alkaline phosphatase level
IVC-gram	7	7	IVC obstruction
SVC-gram	5	5	Right atrial tumor
Two-dimensional echocardiography, heart	6	6	Right atrial tumor
Coronary arteriography	5	2	Severe CAD
Brain scan	3	0	. . .
Bronchoscopy	1	0	. . .
Thoracentesis	1	0	. . .
V/Q scan	1	0	. . .

*CT indicates computed tomography; MRI, magnetic resonance imaging; IVC-gram, inferior venacavography; SVC-gram, superior venacavography; and V/Q scan, ventilation perfusion of the lung.

†IVC indicates inferior vena cava; RUL, right upper lobe of the lung; CAD, coronary artery disease.

no brain wave activity is evident on the electroencephalogram, extracorporeal circulation is discontinued. Tourniquets are secured around the SVC cannula and the infrarenal IVC, and an oblique right atriotomy is performed. Blood volume may be partially exsanguinated into the venous reservoir to minimize back bleeding. Friable tumor is removed, with care taken to prevent any fragments from entering the right ventricle or pulmonary artery.

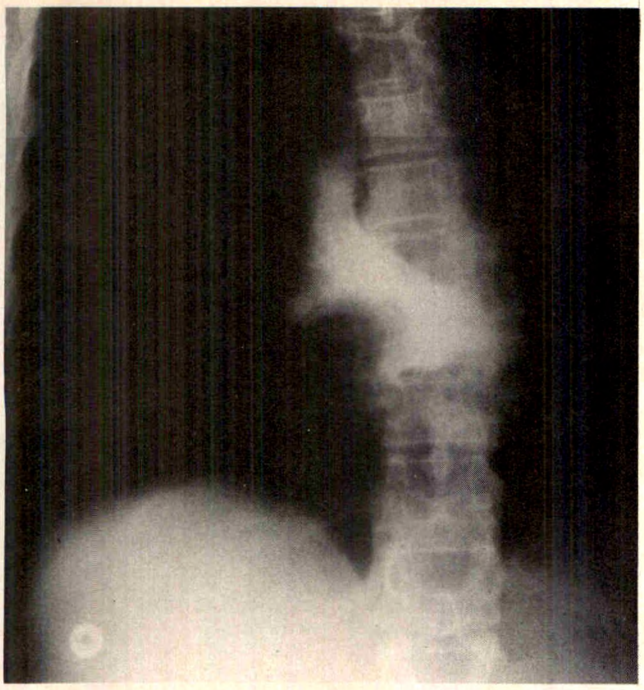
When the right atrial tumor has been extracted, the intracaval component is approached from both the atriotomy and the cavotomy. The renal vein attachment to the IVC is incised, which often necessitates removal of a small portion of IVC wall. Intracaval tumor can then be removed under direct vision, including extensions into the hepatic veins. Direct inspection from the atriotomy above and from the venacavotomy below confirms complete removal of the tumor. The operative field is irrigated copiously.

When the tumor is removed, circulatory arrest is no longer needed. The IVC is occluded with a tourniquet or vascular clamp placed either at the cavoatrial junction or, if the venacavotomy is short, just below the hepatic veins. This tourniquet and another placed below the level of the renal veins permit vascular isolation of the venacavotomy during primary or patch reconstruction of the IVC. Cardiopulmonary bypass is then reinstituted, and the patient is rewarmed slowly at a rate not exceeding 1°C every 3 minutes. The temperature gradient between the perfusate and the patient's core temperature should be less than 10°C. Air is evacuated from the right atrium, and the right atriotomy is closed with a continuous 4-0 polypropylene (Prolene, Ethicon Inc, Somerville, NJ) suture.

If back bleeding impedes precise closure of the IVC, either temporary occlusion of the portal triad (Pringle maneuver) or a short second period of circulatory arrest may be necessary. When the IVC is of adequate size, an alternate method is to apply a partial occluding side clamp to the IVC.

Although the tumor thrombus usually extends only cephalad within the IVC, tumor or benign thrombus may occasionally propagate retrograde into one or both iliac veins.[1,2] Catheter thrombectomy of the iliac veins may be performed, although the clot may reaccumulate. Placement of a DeWeese clip below the remaining renal vein, as performed in two of our patients, may obviate any further concern regarding the need for anticoagulation or transvenous IVC interruption, especially when there has been extensive iliac thrombosis.

If stones are palpated in the gallbladder or if extensive trauma to this organ occurs intraoperatively, elective cholecystectomy may be indicated. Our indications for concomitant coronary revascularization include symptomatic coronary artery disease and asymptomatic left main or multivessel coronary disease of a severity that, if untreated, might increase the risk of perioperative myocardial infarction. When a coronary bypass operation has been planned, it should be performed during rewarming of the patient from deep hypothermia. Distal bypasses are not performed before this time to avoid cardiac manipulation and tumor embolization. After the completion of rewarming and any distal bypass operation, warm blood cardioplegic solution is administered into the aortic root and vein bypass grafts. When the patient's core temperature has been raised to 28°C to 32°C, the cross clamp is removed. When the heart is beating vigorously at normo-



Superior venacavogram demonstrates large right atrial filling defect (tumor extension).

thermic conditions, cardiopulmonary bypass is discontinued. Inotropic drug support may be necessary, particularly when large doses of thiopental sodium have been given. Extensive transfusions of blood, fresh-frozen plasma, and platelets are often required.

RESULTS

Specific details of the operative procedures, pathologic findings, and postoperative complications are listed in Table 3, and blood product usage is listed in Table 4. There were no postoperative myocardial infarctions, strokes, or instances of acute renal failure that necessitated dialysis. Patients were discharged from the hospital a median of 17 days after operation (range, 10 to 30 days).

Complete follow-up information on all seven patients was obtained. Two patients died of metastatic disease: one (the patient with preoperative evidence of a metastatic lung nodule) with ascites and lung metastases at 7 months and one with lung, liver, and spine metastases at 12 months. One patient was alive with lung and spine metastases 34 months after the operation. Four patients were alive without evidence of recurrent disease at 4, 10, 16, and 39 months, although the latter patient has recently been found to have a malignant rectal polyp unrelated to the renal cancer. Of the three other patients who underwent resection in which standard cardiopulmonary bypass was used, one patient died on the eighth postoperative day, and two patients died of diffuse metastases 4 and 17 months after their operations.

COMMENT

Hypernephroma extends to the IVC in 5% to 10% of patients.[2-8] Such extension occurs most frequently in men with right-sided renal tumors and more often results in complete rather than partial obstruction.[2-4,9-12] The IVC extension is a mixture of viable tumor and benign thrombus, but it rarely invades the vascular endothelium.[2,3,6] This latter fact makes resection of such intravascular extensions possible in most patients. Inferior vena caval obstruction is clinically asymptomatic in 50% to 75% of patients because the obstruction is either incomplete or has occurred gradually enough to permit collaterals to develop via the lumbar, azygos, or hemiazygos systems.[2,6,7,11,13,14] More than 50% of such patients may have no other detectable sites of metastatic disease.[4,7,11,14] Numerous reports have demonstrated that in the absence of distant metastases, positive lymph nodes, or perinephric fat invasion, a 5-year survival rate in excess of 50% can be achieved with resection of the primary tumor and IVC extensions.[4,6,9-11,13,15]

Ultimately, intracaval tumor may propagate cephalad to the right atrium or even to the right ventricle. This occurs in 7% to 43% of patients with tumor involving the IVC.[2-4,7,8,10] In our experience approximately 14% of patients with IVC tumor thrombus have had extension to the heart. As with IVC tumor thrombi, atrial extensions are often asymptomatic. However, certain manifestations occur uniquely or with greater frequency when infra-atrial extension is present. These include pulmonary emboli, intermittent tricuspid valve obstruction, right-sided congestive heart failure, and atrial arrhythmias.[2,16,17]

The diagnosis of right atrial tumor thrombus must be suspected in any patient who has a high suprahepatic extension of IVC tumor demonstrated on computed tomography, magnetic resonance imaging, or inferior venacavography. Two-dimensional echocardiography and superior venacavography (Figure) can confirm the diagnosis. Laboratory investigation is often unrevealing, although six of our seven patients did have an elevated alkaline phosphatase level despite normal liver scan results. Cardiologic evaluation and noninvasive carotid artery evaluations are performed to assess the need for concomitant coronary revascularization or carotid endarterectomy at the time of the removal of intracardiac tumor. Patients are evaluated carefully for evidence of metastatic disease, concentrating on likely sites of metastases, including the liver, lung, retroperitoneal lymph nodes, and bone. Surgical resection is contraindicated in the presence of metastatic disease.

Approximately 50 cases of patients with right atrial extensions of renal cell carcinoma have been reported.* Despite the advanced level of transvenous tumor propagation in these patients, enthusiasm for surgical resection has been bolstered by the results of operative treatment of infra-atrial extensions of tumor to the IVC. In addition to the possibility of prolonged survival, patients thus treated are relieved of the general debilitation, discomfort, and hematuria associated with a large renal tumor, the symptoms resulting from IVC obstruction, and cardiac symptoms, including congestive heart failure and atrial arrhythmias. The patient is spared the imminent life-threatening complications of pulmonary embolization, sudden total obstruction of the IVC with circulatory collapse and acute tricuspid valve obstruction.[2,17]

Early attempts to remove such tumors from the right atrium consisted of "blind" retrograde extraction from the venacavotomy.[6,13,22,29] Because this technique did not provide any direct visualization of the tumor, incomplete tumor removal or embolization was possible. Cardiopulmonary bypass was subsequently added by some surgeons. This facilitated retrograde removal of tumor and also permitted a direct approach to the right atrium.† However, even when extracorporeal circulation and the Pringle maneuver are employed, bleeding from hepatic and lumbar veins may be significant. This results in poor visualization of the plane between tumor and vascular endothelium, making precise removal of tumor from the hepatic veins, IVC, and right atrium impossible. Furthermore, the possibility of tumor embolization to the

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*References 6-8, 10, 12, 13, 15, 16, 18-30.

†References 7, 8, 10, 18-21, 23, 25, 28, 30.

Table 3.—Operative Management*

Patient (Date of Operation)	Duration of Procedure				Perinephric Fat†	Nodes	Ancillary Procedures‡	Complications	Postoperative Hospital Stay, d
	Operation, h	Extracorporeal Circulation, min	Aortic Cross Clamping, min	Total Circulatory Arrest, min					
1 (4/17/86)	Indeterminate	54	46	10	–	–	. . .	Transient jaundice	10
2 (8/4/86)	9	76	61	22	–	–	DeWeese clip	. . .	10
3 (9/19/86)	15	121	80	38	?	–	. . .	Transient jaundice, low cardiac output, nonoliguric azotemia, leukocytosis (?)	22
4 (4/13/87)	13	210	135	20	+	–	CAB × 3, cholecystectomy	Low cardiac output, atrial arrhythmias, leukocytosis (?)	17
5 (3/28/88)	10	109	79	13	–	?	DeWeese clip, splenectomy	Atrial arrhythmias, low cardiac output, leukocytosis (?)	13
6 (9/16/88)	11	115	90	19	+	–	CAB × 2, cholecystectomy	Atrial arrhythmias, aspiration pneumonia, prolonged intubation, ileus, urinary tract infection	30
7 (3/7/89)	10	91	46	33	+	?		Transient jaundice, acute cholecystitis (cholecystectomy), coagulopathy	23

*The mean ± SEM length of operation was 11.3 ± 0.9 hours; extracorporeal circulation, 110 ± 19 minutes; aortic cross clamping, 77 ± 12 minutes; total circulatory arrest, 22 ± 4 minutes; and postoperative hospital stay, 17.9 ± 2.8 days.

†Plus sign indicates the presence of fat invasion or nodal metastasis; minus sign, the absence of detectable fat invasion or nodal metastasis; and question mark, the pathology report did not specifically record this data.

‡CAB × 3 indicates triple coronary bypass; CAB × 2, double coronary bypass.

Table 4.—Mean Perioperative Blood Product Use

Blood Product	No. of Blood Units, Mean ± SD (Range)	
	All Patients (n = 7)	Patients Without Coagulopathy (n = 6)
Autologous packed cells	10.7 ± 7.6 (0-56)	3.2 ± 0.8 (0-6)
Packed cells	21.0 ± 4.1 (8-36)	18.5 ± 3.8 (8-33)
Fresh-frozen plasma	14.1 ± 4.4 (4-36)	10.5 ± 2.9 (4-23)
Platelets	18.6 ± 6.2 (6-54)	12.7 ± 2.2 (6-20)
Cryoprecipitate	10 (1 patient)	. . .

tricuspid valve, right ventricle, and pulmonary artery remains, and air embolism may occur through the open IVC.

The most recent technical innovation for the removal of cavoatrial tumors has been the use of total hypothermic circulatory arrest. This was employed initially in the removal of right atrial extensions of Wilms' tumor[17] and has recently been applied to cavoatrial hypernephroma, with low morbidity and mortality.[15,24,26,27,31,32] This technique can be used through either a thoracoabdominal approach or sternotomy combined with midline or subcostal laparotomy. Because the patient is tilted to the left, the former approach may increase the risk of acute tricuspid valve obstruction.[17,19] Circulatory arrest can be achieved with minimal preliminary manipulation of the heart and IVC. This permits a completely bloodless operative field with precise visualization of cavoatrial and hepatic vein tumor and minimizes the risk of air or tumor embolization.

We attribute our low perioperative morbidity and mortality to the use of short periods of circulatory arrest, limited only to that time necessary to see and remove intracaval and intra-atrial tumor. Vena cava reconstruction is performed with local vascular control while reinstituting bypass.[1]

Perioperative use of blood products was substantial in our patients. The mean values (Table 4) are skewed by one patient who had a major postoperative coagulopathy. Most blood loss occurred during retroperitoneal dissection and resulted from a combination of bleeding from tumor neovascularization and venous collaterals from the IVC obstruction. Many of the transfusions of red blood cells were necessitated by dilutional anemia resulting from crystalloid replacement of "third-space" losses. There were no instances of massive uncontrolled bleeding, and the need for fresh-frozen plasma and platelets appeared to result primarily from dilutional coagulopathy. Preoperative angioinfarction can reduce bleeding from tumor neovascularization, although we have not used this technique routinely. Although contraindicated in most surgical procedures for cancer, intraoperative autotransfusion was employed in six of our seven patients because tumor was already present within the vascular system (IVC and right atrium) preoperatively. Autotransfusion was not used, however, during the actual removal of friable tumor from the IVC or right atrium.

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Discussion

JEREMY R. MORTON, MD, Portland, Me: I am impressed by the magnitude of the surgery you have used for this disease. In Maine, we have tried to simplify the bypass part of the procedure as much as possible and found that tumors of this sort can be removed quite effectively using femoral vein and SVC cannulations for venous return and avoiding both hypothermia and aortic cross clamping. There is a brief rush of blood when the caval extension of the tumor is delivered into the atrium but this can be aspirated and returned to the pump and the IVC can be promptly controlled at the atrium with a tourniquet. When the tumor does not extend into the atrium, we have used a centrifugal pump to bypass from the femoral vein to the right atrium without the need for heparin sodium. Since the tumor never seems to involve the vena cava above the level of the renal vein, we have never felt the need to expose the entire retrocaval portion of the vena cava as described here.

THOMAS J. VANDER SALM, MD, Worcester, Mass: Dr Shahian has described a series of seven patients requiring seven extraordinary operations, in whom he attained seven extraordinary results. My own series of patients with this problem is somewhat smaller. So I am unfettered by any of the usual constraints imposed on a discussant who might have had some experience with the subject. But by anybody's standard the accomplishment of Shahian et al is exceptional. No deaths or serious complications with any operation is an enviable record, and all the more so when the disease and its necessary operation are so formidable. Although I have had no direct involvement with these patients, my thoracic surgery colleagues, in conjunction with our urologists, have operated on three similar patients, leading to worse results than, but similar conclusions to, those presented by Dr Shahian. Two of my patients had renal cell carcinoma climbing up the IVC to the right atrium, and one patient had adrenal carcinoma performing similar mischief. Only one patient was operated on using total circulatory arrest, and only he survived the hospitalization.

Dr Shahian has discussed in detail the courses of 7 patients, but 10 are mentioned in the body of the article. I am curious about the clinical course and outcome of the other 3 patients. I presume they were treated without total circulatory arrest. I wonder how this affected the outcome. I also note that of these 7 patients, only 5 had superior venacavography and 6 had cardiac two-dimensional echocardiography. How was the diagnosis of right atrial tumor made in the remaining 1 or 2 patients?

Should all patients with renal cell carcinoma undergo venacavography or are other noninvasive tests sufficient to rule out invasion of the IVC? Two patients in this series had concomitant coronary artery bypass grafts. Should all patients with atrial extension of the tumor undergo preoperative coronary angiography? If not, what are its indications? You mention in the report the need for carotid evaluation. Under what circumstances would you consider concomitant carotid endarterectomy or would a prior-staged carotid endarterectomy be preferable? Finally, if tumor invades the IVC rather than just extending up inside it, do you peel the tumor off or do you resect the IVC? If the latter, with what do you reconstitute the IVC?

FRANK J. LEPREAU, MD, Westport, Mass: Dr Shahian mentioned that one patient had a preoperative known metastasis in the lung, but that was one of the contraindications he mentioned later. If that were true, after the patient recovered from the 11 hours of operation, in a week or so they could have taken out that metastasis. To my knowledge, the very first lobectomy for metastatic cancer was done in 1933 by Dr E. D. Churchill in a patient of Dr J. D. Barney, who a year before had performed a left nephrectomy for renal cell carcinoma (Wilkins E, Head JM, Burke JF. *Am J Surg*. 1978;135:480). The lung shadow was known at the time of the nephrectomy. The patient lived 23 years to die of a myocardial infarction at age 78 years.

DR SHAHIAN: With respect to Dr Vander Salm's question about our three patients operated on previously with standard bypass techniques, one of them died 8 days postoperatively from intraoperative complications; of the other two patients, one died at 4 months and one at 17 months postoperatively of metastatic disease. I should also mention that in addition to the patients presented here, there were two other patients who we've operated on using the circulatory arrest technique. One was a very elderly gentleman with a suprahepatic infracardiac tumor, who survived surgery but subsequently developed a number of complications in the hospital and died 4 months postoperatively. The second patient had an adrenal carcinoma extending to the heart, and she is alive 17 months after resection.

With respect to the question of echocardiography vs superior venacavography, the numbers you mentioned were overlapping. Every patient underwent either superior venacavography or two-dimensional echocardiography of the heart to make a diagnosis of cardiac involvement. We were fooled in one patient with magnetic resonance imaging, and I'm unwilling to trust this modality alone to diagnose cardiac involvement. Should every patient have venacavography? I think the resolution of magnetic resonance imaging is getting to the point that I would almost be willing to operate on these patients without an inferior venacavogram.

Who needs preoperative coronary arteriography? Most of these patients are unable to perform well enough on an exercise test to get an accurate noninvasive assessment of their coronary status. We have been doing coronary arteriography in all these patients. Given the dramatic volume and blood pressure changes observed during many of these operations, uncorrected severe coronary lesions might result in perioperative infarction. Because tumor removal necessitates cardiopulmonary bypass anyway, the addition of coronary bypasses to the procedure is not difficult.

Carotid noninvasive studies are performed on all patients. This poses the same dilemma we face in coronary bypass surgery, ie, who gets concomitant carotid revascularization? Certainly the symptomatic patient or a patient with bilateral severe lesions, particularly one side occluded and one severely stenosed, would benefit. The need for carotid endarterectomy in a patient with an asymptomatic unilateral tight carotid stenosis would have to be assessed on an individual basis.

Finally, what happens if tumor invades the IVC? We've not had that experience. That happens very rarely. If it were a localized area of invasion, we would try to resect it and repair it with a pericardial patch. We have no experience with other types of replacement, although some groups have reported the use of thin polytef (Gore-Tex, W. L. Gore and Associates Inc, Flagstaff, Ariz).

Dr Morton, why use circulatory arrest? The problem with any kind of standard bypass technique or nonbypass technique is that even with local occlusion above and below the retrohepatic portion of the cava, and with the Pringle maneuver, you still have back bleeding from the hepatic veins as well as from the lumbar and vertebral veins. This makes visualization of the hepatic veins impossible, and the tumor really cannot be cleared out adequately. We don't really believe that 77 minutes of aortic cross clamping is an excessive period today with adequate myocardial protection, and we have not experienced any complications that we could specifically attribute to hypothermic arrest.

Finally, Dr Lepreau, we currently would not operate on a patient who had a preoperative lung metastasis. Why didn't we take out the lung metastasis after we had taken out the kidney tumor in our patient? By the time he had recovered enough to undergo that operation, several other sites of metastatic disease were present, and obviously it was impossible to do him any further good with resection.

In Other AMA Journals

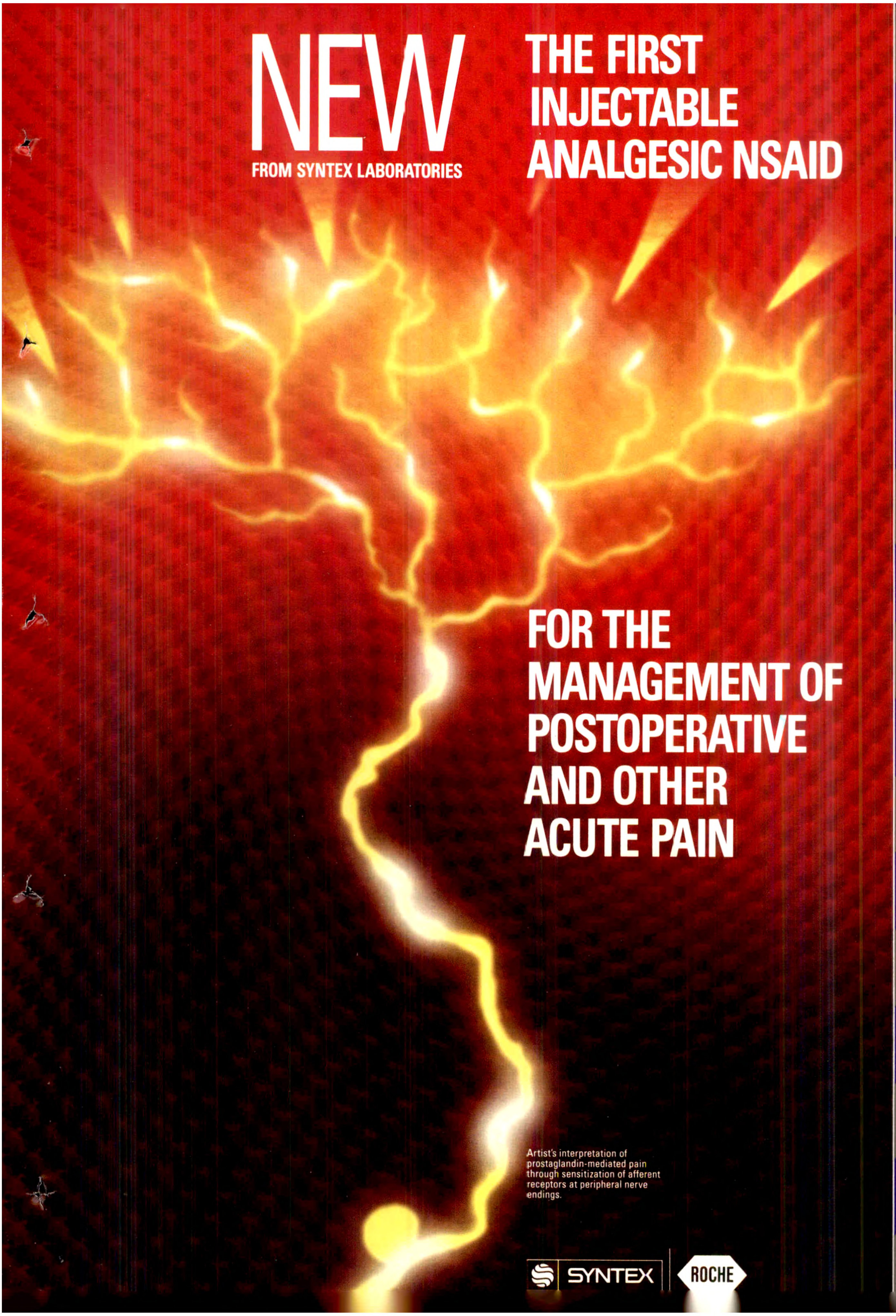
ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Lectin Histochemistry and Ultrastructure of Medullary Carcinoma of the Thyroid Gland

Manuel Sobrinho-Simoes, MD; Clara Sambade, MD; Jahn M. Nesland, MD; Ruth Holm, PhD; Ivan Damjanov, MD

Lectin histochemistry and electron microscopy were used to study a series of 13 solid or microacinar medullary carcinomas of the thyroid (MCTs) and compare them with four follicular MCTs and other forms of thyroid cancer. Lectin histochemistry was not found to be of diagnostic value, since the MCT did not display any distinct lectin-binding pattern. This approach demonstrated that all MCTs, irrespective of their histologic appearance, consist of polarized cells, arranged into microfollicles that can be demonstrated readily by electron microscopy. We conclude that all MCTs form follicles, some visible by light microscopy, while others are submicroscopic and apparent only on histochemical staining. Because of the histochemical and ultrastructural similarities between solid MCTs and tumors with a follicular pattern, the latter should not be considered a distinct variant of C-cell neoplasia (*Arch Pathol Lab Med*. 1990;114:369-375).

Reprint requests to Department of Pathology, Medical Faculty, Hospital S. Joao, 4200 Porto, Portugal (Dr Sobrinho-Simoes).



NEW
FROM SYNTEX LABORATORIES

THE FIRST INJECTABLE ANALGESIC NSAID

FOR THE MANAGEMENT OF POSTOPERATIVE AND OTHER ACUTE PAIN

Artist's interpretation of prostaglandin-mediated pain through sensitization of afferent receptors at peripheral nerve endings.

SYNTEX | ROCHE

Artist's interpretation of pain relief through reduction of prostaglandin levels that reduces the sensitivity of afferent receptors at peripheral nerve endings.

TORADOL® IM

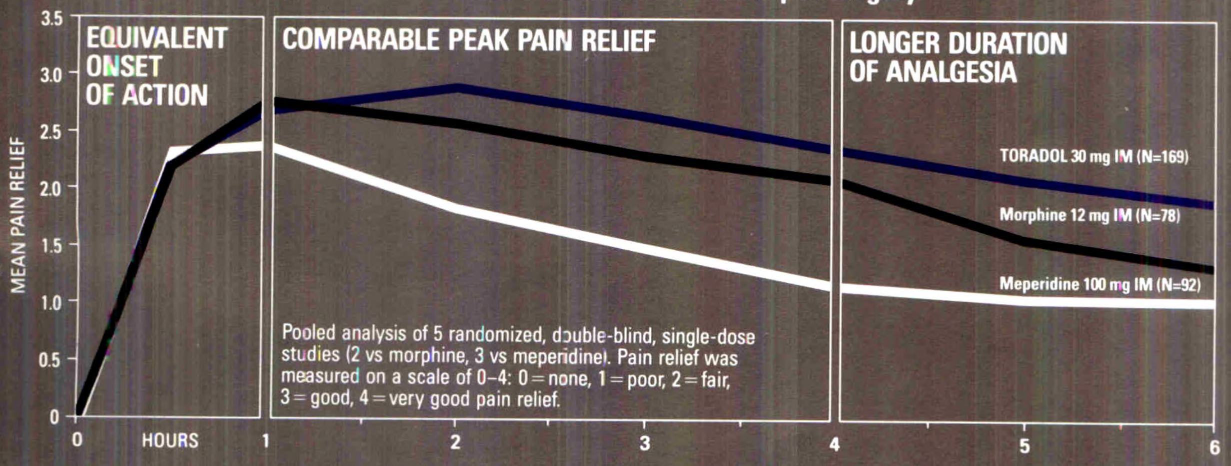
INJECTION

(KETOROLAC TROMETHAMINE) 15, 30, 60 MG

NARCOTIC EFFICACY WITHOUT NARCOTIC DRAWBACKS*

The first peripherally acting analgesic with efficacy comparable to morphine 12 mg and meperidine 100 mg

Analgesic efficacy of TORADOL IM administered 24–72 hours postsurgery[1]



Pooled analysis of 5 randomized, double-blind, single-dose studies (2 vs morphine, 3 vs meperidine). Pain relief was measured on a scale of 0–4: 0 = none, 1 = poor, 2 = fair, 3 = good, 4 = very good pain relief.

Documented efficacy following a broad range of surgical procedures:

General, orthopaedic, gynecologic (not for obstetric use)

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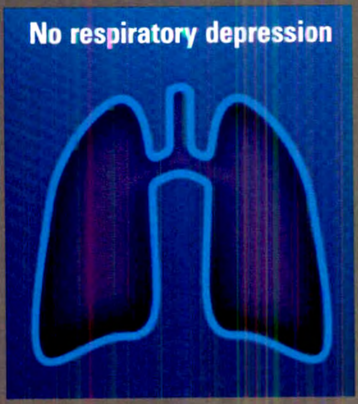
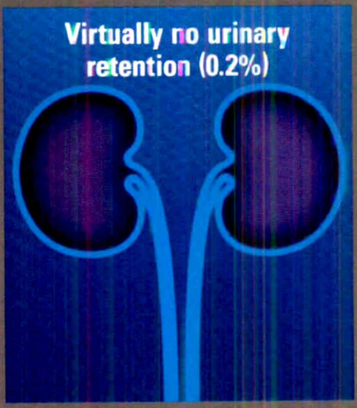
*As with other nonsteroidal drugs, the most frequently reported side effects are gastrointestinal, with some GI symptoms reported by 3–9% of patients in clinical trials. See "Warnings" and "Precautions" sections of prescribing information.

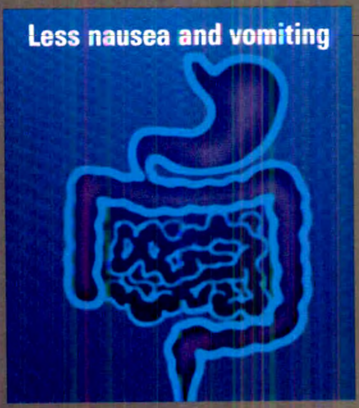
[1] Data on file, Syntex Laboratories, Inc., Document #90037-1.

Please see brief summary of prescribing information on last page of this advertisement.

Less CNS impairment


No respiratory depression

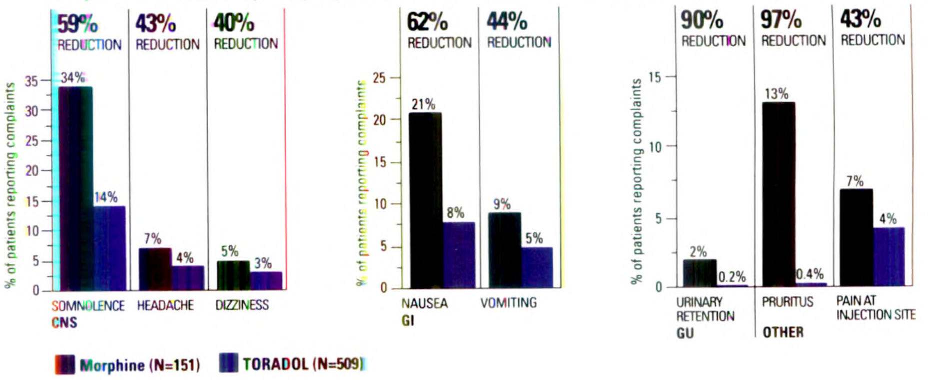

Virtually no urinary retention (0.2%)


Less nausea and vomiting

START RECUPERATION WITHOUT NARCOTIC SIDE EFFECTS[1*]

- 62% less nausea and 44% less vomiting
- 48% fewer CNS side effects
- No respiratory depression
- No hypotension
- 1-day earlier resumption of normal bowel function following major abdominal surgery
- No difference in clinically significant postoperative bleeding with TORADOL IM (0.4%) as compared to opiates (0.2%)

Comparison of most frequently reported side effects in 2 multi-dose studies (TORADOL IM vs morphine)**



Adverse reactions rates from short-term use of NSAIDs are generally from 1/2 to 1/10 the rates associated with chronic usage. This is also true for TORADOL IM.

FOR POSTOPERATIVE AND OTHER ACUTE PAIN

NEW

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*As with other nonsteroidal drugs, the most frequently reported side effects are gastrointestinal, with some GI symptoms reported by 3–9% of patients in clinical trials. See "Warnings," "Precautions," and "Adverse Reactions" sections of prescribing information.

**Most frequently reported side effects in major body systems with the exception of the cardiovascular system. 2% of patients treated with Toradol reported vasodilation as compared to 1% of patients treated with morphine.

1. Documented in 2 randomized, double-blind, multi-dose studies in which 509 patients received ketorolac 30 mg and 151 patients received morphine 10 mg or morphine 12 mg. Bowel function was evaluated in a subset of 47 patients undergoing gastric bypass surgery. Data on file, Syntex Laboratories, Inc., Document #90037-2.
2. Data on file, Syntex Laboratories, Inc., Document #90037-3.

Please see brief summary of prescribing information on last page of this advertisement.

Analgesic therapy well suited for postoperative use

TORADOL IM is not an opiate

- Does not act on opiate receptor sites
- No potential for abuse
- No special restrictions or controls required

May be an appropriate alternative to narcotics for:

- Patients with narcotic allergy or intolerance
- Patients with a history of, or potential for, drug abuse or dependence

Special advantages may facilitate postoperative recuperation

- Patients with COPD or the obese—no negative effects on pulmonary function
- Ambulatory surgery patients—less CNS impairment (e.g., 59% less somnolence and 40% less dizziness)

Optimize analgesia on the day of surgery

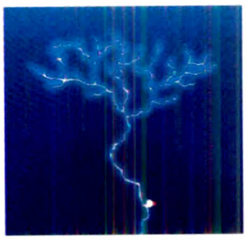
- On the day of surgery, some TORADOL IM patients may require supplemental narcotics if pain relief is inadequate 1–2 hours after dosing
- On average, only one supplemental dose of narcotics may be required[2]

TORADOL® IM
INJECTION

(KETOROLAC TROMETHAMINE) 15, 30, 60 MG

NARCOTIC EFFICACY WITHOUT NARCOTIC DRAWBACKS*

FOR POSTOPERATIVE AND OTHER ACUTE PAIN



NEW TORADOL® IM INJECTION

(KETOROLAC TROMETHAMINE) 15, 30, 60 MG

OPTIMIZE ANALGESIC THERAPY FOR THE POSTOPERATIVE PATIENT

PROPER DOSAGE POSTOPERATIVELY

For maximum analgesia:

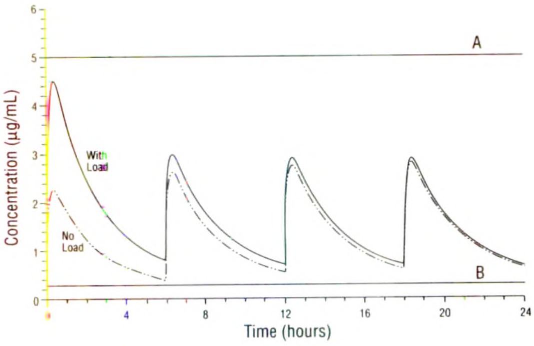
- Give patients prompt pain relief: start with loading dose of 60 mg IM
- Follow with maintenance dose of 30 mg IM Q6h to control pain
- The recommended maximum total daily dose is 150 mg for the first day and 120 mg/day thereafter*

Simulated incremental plasma concentrations after 2 multi-dose regimens: (1) TORADOL$^{\mathrm{IM}}$ 30 mg Q6h (no load); (2) TORADOL$^{\mathrm{IM}}$ 60 mg LOADING DOSE followed by 30 mg Q6h

A = Plasma concentration above which side effects are more frequent

B = Estimated concentration required to obtain 50% decreases in pain intensity scores in dental surgery pain

Achieve optimal peak and trough plasma levels by starting with a loading dose (e.g., 60 mg), while maintaining plasma levels within the recommended therapeutic range. Follow with maintenance doses (e.g., 30 mg every 6 hours) to keep plasma levels in the optimal range.



Patient Selection: Use in patients with moderate-to-severe postoperative pain following general, orthopaedic, or gynecologic surgery (not for obstetric use)

Lower doses:

- Recommended for patients under 50 kg (110 pounds), patients over 65 years of age, and patients with reduced renal function
- Start with loading dose of 30 mg IM
- Follow with maintenance dose of 15 mg IM Q6h to control pain

On the day of surgery, some TORADOL$^{\mathrm{IM}}$ patients may require supplemental narcotics if pain relief is inadequate 1–2 hours after dosing (not compatible in same syringe)

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*Dosages above those recommended are not associated with commensurate increases in efficacy.

Please see brief summary of prescribing information on last page of this advertisement.

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SYNTEX

ROCHE

TORADOL® IM (ketorolac tromethamine)

Brief Summary
TORADOL is a nonsteroidal anti-inflammatory drug (NSAID). TORADOL 15 mg/mL solution contains 10% (w/v) alcohol, USP, and 6.68 mg sodium chloride in sterile water. The 30 mg/mL solution contains 10% (w/v) alcohol, USP, and 4.35 mg sodium chloride in sterile water. The pH is adjusted with sodium hydroxide or hydrochloric acid. **Indications and Usage:** Indicated for the short-term management of pain. Not recommended for use as an obstetrical preoperative medication or for obstetrical analgesia because it has not been adequately studied and because of the known effects of NSAIDs on uterine contraction and fetal circulation. Not recommended for routine use with other NSAIDs because of the potential for additive side effects. TORADOL protein-binding is affected by aspirin but not by acetaminophen, ibuprofen, naproxen or piroxicam. Studies with other NSAIDs have not been done. Has been used concomitantly with morphine and meperidine without adverse interactions. **Contraindications:** Do not use in patients with hypersensitivity to ketorolac or with the complete or partial syndrome of nasal polyps, angioedema, and bronchospastic reactivity to aspirin or other NSAIDs. **Warnings:** Although TORADOL Injection is recommended for short-term use only, long-term administration of oral ketorolac has shown that this drug shares the risks of other NSAIDs when taken chronically. Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Remain alert for ulceration and bleeding in such patients, even in the absence of previous GI tract symptoms. In clinical trials, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for 1 year. Inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. Studies have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events, and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than others and most spontaneous reports of fatal GI events are in this population. High doses of an NSAID probably carry a greater risk of these reactions. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity. **Precautions:** Impaired Renal or Hepatic Function: As with other NSAIDs, use with caution in patients with impaired renal or hepatic function, or a history of kidney or liver disease. Renal Effects: As with other NSAIDs, long-term administration to animals resulted in renal papillary necrosis and other abnormal renal pathology. In humans, hematuria and proteinuria have occurred in long-term trials with oral ketorolac with a frequency and degree similar to aspirin. A second form of renal toxicity has been seen in patients with conditions leading to a reduction in blood volume and/or renal blood flow. In these patients, an NSAID may precipitate overt renal failure. Patients at greatest risk are those with impaired renal function, heart failure, liver dysfunction, taking diuretics, and the elderly. Discontinuation of the NSAID is typically followed by recovery. Use with caution in patients with impaired renal function as reduced creatinine clearance results in reduced clearance of the drug. Follow such patients closely. Fluid Retention and Edema: These have been reported with NSAIDs; use TORADOL with caution in patients with cardiac decompensation, hypertension, or similar conditions. Hepatic Effects: With NSAIDs, borderline elevations of liver tests may occur in up to 15% of patients. These may progress, remain unchanged, or disappear with continued therapy. Elevations of ALT (SGPT) or AST (SGOT) occurred in clinical trials with oral ketorolac in less than 1% of patients. Evaluate a patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, for evidence of a more severe hepatic reaction. Hematologic Effects: TORADOL inhibits platelet aggregation and may prolong bleeding time but does not affect platelet count, prothrombin time (PT) or partial thromboplastin time (PTT). Carefully observe patients with coagulation disorders or who are receiving drug therapy that interferes with hemostasis. Inhibition of platelet function by TORADOL disappears within 24-48 hours after the drug is discontinued. In clinical studies, the incidence of clinically significant postoperative bleeding was 0.4% compared to 0.2% in the groups receiving opiates. **Drug Interactions:** TORADOL is highly bound to plasma protein (mean 99.2%), independent of concentration. In vitro binding of warfarin to plasma proteins is slightly reduced by TORADOL (99.5% control vs 99.3% with TORADOL 5-10 μg/mL). TORADOL does not alter digoxin protein binding. At therapeutic concentrations of salicylate (300 μg/mL), in vitro binding of TORADOL was reduced from 99.2% to 97.5%, a potential 2-fold increase in unbound TORADOL plasma levels; hence, use TORADOL with caution (or at a reduced dosage) in patients being treated with high dose salicylate regimens. Therapeutic concentrations of digoxin, warfarin, ibuprofen, naproxen, acetaminophen, phenytoin, tolbutamide and piroxicam did not alter TORADOL protein binding. In a study of 12 healthy volunteers given TORADOL 10 mg orally for 6 days prior to co-administration of a single dose of warfarin 25 mg, no significant changes in pharmacokinetics or pharmacodynamics of warfarin were detected. In another study of 12 healthy volunteers, co-administration of heparin 5000 U s.c. and TORADOL did not show any pharmacodynamic effects of the combination on template bleeding time or kaolin cephalin clotting time. There is no evidence that TORADOL induces or inhibits the hepatic enzymes capable of metabolizing itself or other drugs. Some NSAIDs inhibit renal lithium clearance, leading to increased plasma concentration. This has not been studied with TORADOL. Some NSAIDs reduce the clearance of methotrexate, enhancing its toxicity. This has not been studied with TORADOL. TORADOL has been administered concurrently with morphine in clinical trials without adverse interactions. **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Studies in mice and rats at oral doses equal to or 2.5 times the parenteral MRHD (Maximum Recommended Human Dose), respectively, showed no evidence of tumorigenicity. Ketorolac was not mutagenic in tests with S. typhimurium, S. cerevisiae, or E. coli and did not cause chromosome breakage in the in vivo mouse micronucleus assay. Impairment of fertility did not occur in male or female rats at oral doses 4.5 and 8 times the parenteral MRHD, respectively. **Pregnancy: Pregnancy Category B:** Reproduction studies in rabbits and rats with daily oral doses 1.8 and 5 times the parenteral MRHD, respectively, did not reveal evidence of harm to the fetus. Ketorolac caused delayed parturition and dystocia in rats at oral doses higher than the parenteral MRHD, like other NSAIDs. There are no adequate and well-controlled studies in pregnant women. TORADOL should be used during pregnancy only if clearly needed and no known safer alternatives are available. **Labor and Delivery:** TORADOL is not recommended for use during labor and delivery. **Lactation and Nursing:** After a single oral dose of TORADOL 10 mg to humans, the maximum milk concentration was 7.3 ng/mL and the maximum milk-to-plasma ratio was 0.037. After one day of dosing (qid), the corresponding values were 7.9 ng/mL and 0.025. Use caution when TORADOL is administered to a nursing woman. **Pediatric Use:** TORADOL is not recommended for use in children. **Use in the Elderly:** Because ketorolac is cleared more slowly by elderly, who are also more sensitive to renal effects of NSAIDs, use extra caution and reduced dosages when treating the elderly. **Adverse Reactions:** Adverse reaction rates from short-term use of NSAIDs are generally 1/2 to 1/10 the rates associated with chronic usage. This is also true for TORADOL. In studies of patients treated for up to 1 year, the incidence of serious and nonserious ADRs, including GI tract ulceration and bleeding (yearly rate 1.2 to 5.4%), associated with oral ketorolac 10 mg, 1 to 4 times per day prn, was comparable to treatment with aspirin 650 mg prn. Be alert for the usual complications of NSAID treatment. The adverse reactions listed below were reported to be probably related to TORADOL in trials in which patients received up to 20 doses of TORADOL 30 mg IM in 5 days. **Incidence greater than 1%:** Body as a whole: edema. GI: nausea,* dyspepsia,* GI pain,* diarrhea. Nervous system: drowsiness,* dizziness, headache, sweating. Injection site pain was reported by 2% of patients in multidose studies (vs 5% for morphine). *Incidence of reported reaction 3%-9%. Reactions occurring in less than 3% are unmarked. **Incidence 1% or less:** Body as a whole: asthenia, myalgia. Cardiovascular: vasodilation, pallor. Dermatologic: pruritus, urticaria. GI: constipation, flatulence, GI fullness, liver function abnormalities, melena, peptic ulcer, rectal bleeding, stomatitis, vomiting. Hemic and lymphatic: purpura. Nervous system: dry mouth, nervousness, paresthesia, abnormal thinking, depression, euphoria, excessive thirst, inability to concentrate, insomnia, stimulation, vertigo. Respiratory: dyspnea, asthma. Special senses: abnormal taste, abnormal vision. Urogenital: increased urinary frequency, oliguria. **Drug Abuse and Physical Dependence:** TORADOL is not a narcotic agonist or antagonist. Subjects did not show any symptoms or signs of withdrawal upon abrupt discontinuation of IV or IM dosing. Patients receiving TORADOL orally for ≥6 months have not developed tolerance and there is no pharmacologic basis to expect addiction. TORADOL did not exhibit activity in classical animal studies which are reasonable predictors of opiate analgesic action. In vitro, TORADOL does not bind to opiate receptors. Thus, TORADOL does not have central opiate-like activity. **Overdosage:** Lack of experience with acute overdosage precludes characterization of sequelae and assessment of antidotal efficacy. At single oral doses >100 mg/kg in rats, mice and monkeys, symptoms such as decreased activity, diarrhea, pallor, labored breathing, rales, and vomiting were observed. **Dosage and Administration:** TORADOL may be used on a regular schedule or prn, although current recommendations for pain management are to use analgesics on a regular schedule rather than prn based on the return of pain. For the short-term management of pain the recommended initial dose is 30 or 60 mg IM as a loading dose, followed by half of that (15 or 30 mg) every 6 hours as long as needed to control pain. The recommended maximum total daily dose is 150 mg for the first day and 120 mg/day thereafter. The lower end of the dosage range is recommended for patients under 50 kg (110 pounds), for patients over 65 years of age, and for patients with reduced renal function. CAUTION: Federal law prohibits dispensing without prescription.

U.S. Patent No. 4,089,969 and others.

Mfd. for Syntex Laboratories, Inc.
Palo Alto, CA 94304
by Survival Technology, Inc.
Bethesda, MD 20814

SYNTEX

02-2434-40-00 December 1989

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Computerized Topographic Brain Mapping During Carotid Endarterectomy

James R. Elmore, MD; Jens Eldrup-Jorgensen, MD; William H. Leschey, MD; William E. Herbert, MD;
Richard C. Dillihunt, MD; Ferris S. Ray, MD

• Computerized topographic brain mapping processes standard electroencephalographic data and displays it in a color map, thus simplifying interpretation. During a 2-year period, 65 carotid endarterectomies were performed with the use of brain mapping as the sole criterion for shunt placement. Forty-three patients (66%) were found to have abnormal brain maps preoperatively. Ten patients (15%) developed ischemic changes after cross-clamping (all resolved after shunt placement). Postoperative brain maps were unchanged in 54 patients (83%) and improved in 7 patients (11%). A new, small focal abnormality was identified in 4 patients without shunts (6%), none of whom had a change in neurologic status. The overall major morbidity and mortality was 1.5%. Computerized brain mapping is a sensitive and readily interpretable means of monitoring cerebral perfusion during carotid surgery. We found the computerized electroencephalographic data to be a dependable criterion for selective shunting and for confirmation of shunt patency during carotid endarterectomy.

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Electroencephalography (EEG) has been used for years as a means of monitoring cerebral perfusion during carotid endarterectomy.[1] Recently, computerized topographic brain mapping has been developed that translates the EEG wave forms into a color topographic map of brain activity. This new technology is very sensitive and provides easily interpretable data. Intraoperative EEG monitoring and computerized brain mapping have been used primarily by surgeons who perform shunting selectively. Brain mapping can also be used by advocates of routine shunting to assess shunt patency or by routine "nonshunters" to evaluate ischemia during cross-clamp periods. The purpose of this report is to review our experience with the use of brain mapping as a guide for the need for shunt placement and for confirmation of shunt patency during carotid endarterectomy.

PATIENTS AND METHODS

During a 2-year period from May 1987 to September 1989, a total of 64 patients who underwent 65 carotid endarterectomies at the Maine Medical Center, Portland, were studied prospectively with brain mapping used as the sole method for determining placement of an intraluminal shunt. Indications for operation were transient ischemic attacks (TIAs) in 23 patients (35%), amaurosis fugax in 14 patients (22%), previous cerebrovascular accident in 23 patients (35%), and high-grade stenosis in 5 patients (8%). This subgroup of patients with high-grade (>75%) stenosis included two asymptomatic patients and three patients having endarterectomy after surgery on the contralateral carotid for symptoms.

The patients' ages ranged from 40 to 82 years, with a mean of 65 years. Thirty-seven patients (58%) were male and 27 (42%) were female. Associated medical conditions were seen in all patients: coronary artery disease in 39 (61%), hypertension in 32 (50%), lower-extremity peripheral vascular disease in 23 (36%), diabetes in 13 (20%), and documented chronic lung disease in 10 (16%). A smoking history was present in 47 (73%).

A total of eight different surgeons performed these procedures. The average length of stay was 6 days, divided evenly between preoperative evaluation and postoperative care.

All patients underwent preoperative evaluation with both noninvasive Doppler studies and angiography. All patients undergoing operation had either a high-grade stenosis with at least a 75% stenosis (58 [89%] of the cases), moderate stenosis of greater than 50% (three [5%] of the cases), or presence of a significant ulceration (four [6%] of the cases). Contralateral angiographic data consisted of occlusion in six (9%), high-grade stenosis in eight (12%), and moderate stenosis in 15 (23%). The average clamp time for the patients without shunts was 26 minutes, and for the patients with shunts, 35 minutes (including the shunt time).

This study used a computerized topographic brain imager (Neuro-Science Inc, San Diego, Calif). The topographic maps are created from the electrical signals of 28 electrodes. These electrodes are placed according to the international 10-20 system and require 30 to 45 minutes for their application. A statistical calculation called a fast Fourier transform is used to analyze the signals from each of the electrodes and to determine the amplitude in each of the five classic EEG bands. These data are then converted into color maps. Amplitudes between electrodes are interpolated to generate 4096 points of data. Both hemispheres can be displayed together, with the left hemisphere on the left side of the screen or paper and the right hemisphere on the right side (opposite the convention used by radiologists in their images). A spectral map is also generated that describes the predominant frequency level in each area of the brain. Baseline amplitude is set as green. Increased amplitude appears red,

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orange, or yellow, whereas decreased amplitude is represented as blue.

The raw EEG data can also be superimposed over the color maps on the monitor. These wave forms allow the EEG technician to observe for artifacts. The color maps and wave forms are simultaneously presented on the monitor in a real-time fashion. Every 2.5 seconds of EEG data are converted instantly into a new picture. At the conclusion of the procedure, time-averaged maps are created for review by the neurologist. The neurologist may still review the entire record or portions of particular interest from the raw data, which are stored on an optical disk.

A preoperative map is obtained in the awake state either the night before surgery or the morning of surgery. The patient is monitored with brain mapping during the period of induction so that hemodynamic changes or anesthetics that might affect the EEG can be altered by the anesthesiologist as necessary. Barbiturates may be used for induction but it has been our practice to otherwise avoid barbiturates in order to minimize pharmacologically induced changes in the wave form. A new map is obtained at this point, which is used as a baseline for changes that may occur after crossclamping.

After crossclamping, particular attention is paid to the alpha, beta, and theta frequencies. Classification of a change as "new" ischemia in a preexisting abnormality requires an extension into another frequency band or an extension of the spatial distribution into another region of the brain. Focal or global changes are initially evaluated to determine if they are secondary to anesthetic or hemodynamic changes. If the changes cannot be resolved on this basis, they are believed to be due to ischemia and used as an indicator for shunt placement. If no changes are observed, the endarterectomy may be carried out in an unhurried fashion. At the conclusion of the operation, the patient is awakened and extubated in the operating room, and gross neurologic function evaluated. A final postoperative tracing is obtained in the recovery room when the patient is fully awake.

Statistical analysis was carried out with Fisher's Exact Test.

RESULTS

Preoperative brain maps were abnormal in 43 (66%) of the 65 operations. Only 23 (36%) of all patients had experienced a previous cerebrovascular accident, indicating a high incidence of silent perfusion defects. Preoperative abnormalities were found in 20 (87%) of 23 patients with a history of TIAs, 15 (65%) of those with a history of cerebrovascular accident, and seven (50%) of those with a history of amaurosis. One of the two asymptomatic patients had an abnormal preoperative map. All of the patients with TIAs who had evidence of focal areas of ischemia on the preoperative maps were neurologically normal at the time of the preoperative brain map.

Ten patients (15%) developed ischemic changes after carotid crossclamping. The ischemic changes were ipsilateral to the operated-on side in 6 patients and global in 4. All 10 patients underwent shunting, with resolution or marked improvement of the ischemic changes. The abnormalities of the real-time images on the brain mapper were obvious in each case. Patients with a history of stroke developed ischemia with crossclamping as frequently as those without such a history (4 [17%] of 23 vs 6 [14%] of 42; $P = .50$). Patients with an abnormal preoperative brain map developed ischemia significantly more frequently after crossclamping than did those with a normal preoperative map (10 [23%] of 43 vs 0 [0%] of 22; $P < .02$). Shunt patency was confirmed by continued improvement in the brain maps in all patients during the crossclamp period.

Postoperative brain maps were unchanged in 54 patients (83%) and improved in seven patients (11%). These seven patients had improvement in focal areas of decreased activity that had been seen on the preoperative maps. A new, small focal abnormality was identified in four patients without shunts (6%) in the recovery room, all of whom were neurologically unchanged.

There was one death due to an intracerebral hemorrhage. This patient had a focal area of decreased activity in the right temporal region in the preoperative map that did not change with crossclamping and therefore was not shunted. The patient awoke neurologically intact, and the postoperative map was unchanged. Several hours later, the patient became obtunded, and computed tomographic scan disclosed the intracerebral hemorrhage that was believed to be secondary to the hyperperfusion syndrome. Apart from this one death, there were no permanent neurologic deficits. One patient in whom shunting was performed had a transient neurologic deficit. This consisted of an expressive aphasia that was an exacerbation of her preoperative status and resolved by discharge. The overall major morbidity and mortality was 1.5%. Other complications included two cases of cardiac arrhythmia, which were easily controlled, two cases of temporary neuropraxia secondary to retractors, and a single case each of urinary retention, urinary tract infection, and aspiration on induction of anesthesia.

Figure 1 represents a brain map after induction of anesthesia in a 68-year-old man who underwent left carotid endarterectomy for TIAs, with a right internal carotid occlusion. The preoperative maps (not shown) were similar to these maps in that there was decreased activity in the left temporal region. With crossclamping, global ischemia developed, as seen in Fig 2. A shunt was immediately inserted, and there was resolution of these changes with return to a map identical to that seen in Fig 1. The postoperative course was uneventful and the postoperative maps were unchanged, continuing to show the decreased activity in the left temporal region.

COMMENT

Stroke is one of the most dreaded complications of carotid endarterectomy. To minimize this complication, we believe it is important to monitor and maintain cerebral perfusion during the period of carotid crossclamping. The intraluminal shunt has been designed to maximize cerebral blood flow (CBF) and to preserve cerebral perfusion during carotid crossclamping. The indications for use of the shunt are controversial.[2,3]

Part of this controversy is based on the debate over the major cause of perioperative stroke. Routine "nonshunters"[4] believe that the hemodynamic risk of crossclamping has been overstated and that the risk of an embolic stroke caused by a shunt can be avoided with their technique. The technical performance of the endarterectomy is thought to be enhanced by the absence of the intraluminal shunt, providing a better view of the end point. Routine "shunters"[5] disagree and think that the routine use of the shunt decreases the technical problems associated with its use and that it ensures preservation of CBF.

"Selective shunting" attempts to minimize the use of the shunt while preserving maximal cerebral perfusion for those patients who require it. Multiple criteria have been used for selective shunting: (1) clinical history and/or preoperative angiography; (2) internal carotid backflow and/or stump pressure[6]; (3) xenon-measured CBF; (4) continuous EEG or computerized topographic brain mapping; and (5) clinical assessment with the patient under local anesthesia. Of all of these criteria for selective shunting, only EEG, brain mapping, and performance of the procedure with the patient under local anesthesia provide data on cellular function.

The need for a shunt can be based on the results of patients undergoing carotid endarterectomy with local or regional anesthesia. One of the largest series in the literature was reported by Hafner and Evans.[7] They reviewed their experience with 1200 endarterectomies done with local anesthesia

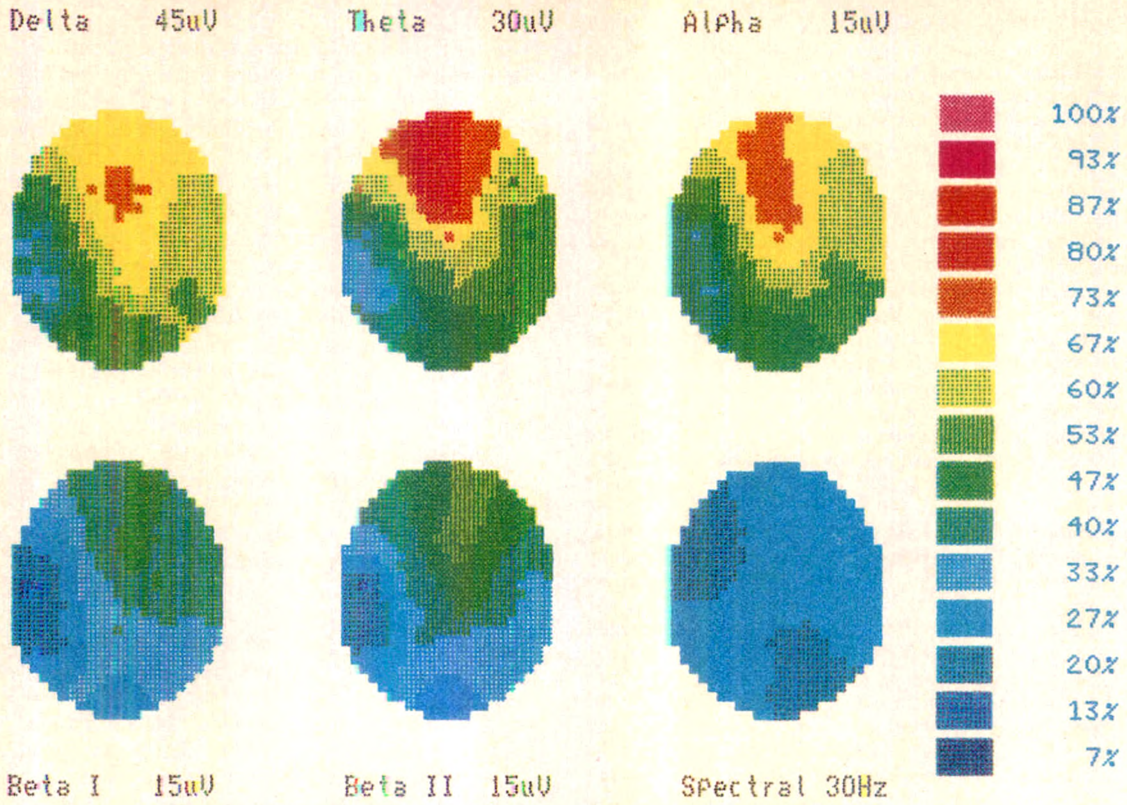

Fig 1.—Baseline maps of a 68-year-old man after induction of anesthesia, with a focal area of ischemia in the left temporal region.

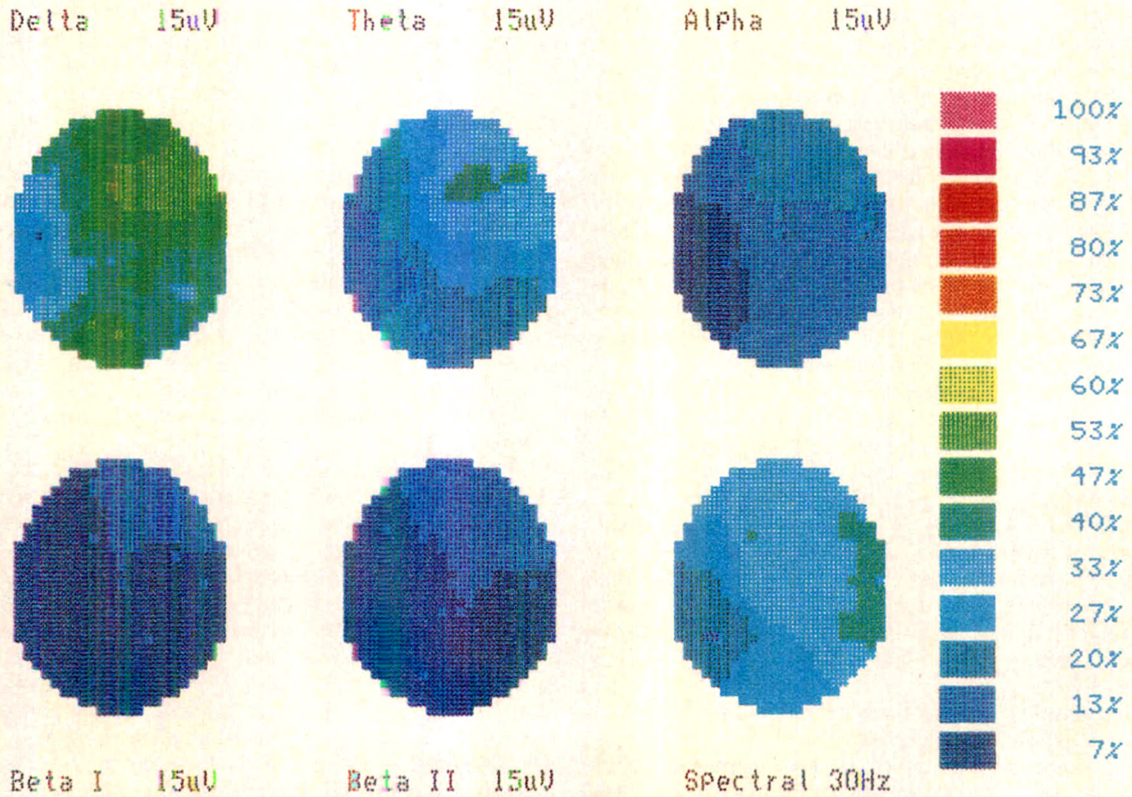

Fig 2.—Brain maps of the same patient as in Fig 1, displaying global ischemia after crossclamping. These changes all resolved after shunting, with return of maps to baseline as in Fig 1.

and found that 113 (9%) of the patients developed neurologic deficits during crossclamping. All 113 patients had resolution of neurologic changes with shunting.

Sundt and associates[8] at the Mayo Clinic, Rochester, Minn, have had a large experience with selective shunting based on EEG monitoring and CBF. In 1986, they reported on 1935 endarterectomies performed during the previous 14 years. Of these patients, 41% received shunts. Kelly and associates[9] reviewed 289 endarterectomies with the use of a shunt based only on an EEG change at the time of crossclamping. Ten percent of the patients developed EEG changes and received shunts. Carotid stump pressures were also measured, and no correlation was found with EEG changes. Whittemore and associates[10] reported a similar experience with 219 endarterectomies. Ischemic changes were identified in 16%, and these patients received shunts. From these last two studies, shunts based purely on EEG changes will probably be used in about 10% to 16% of the patients.

The technique of intraoperative continuous EEG monitoring has been well described.[11] A standard EEG consists of 19 electrodes and represents the data in a wave form. These wave forms are characterized by different frequencies and amplitudes. Anesthetic agents suppress the higher-frequency activity. The same difficulties inherent in standard EEG can also occur with computerized brain imaging. Burst suppression activity can be seen with barbiturates or inhalational anesthetic agents. Relative hypotension can also cause a global suppression of EEG activity. The careful attention to obtaining a stable anesthetic regimen before crossclamping will help avoid confusion between true ischemic changes and these other conditions.

Computerized topographic brain mapping has been shown to be more sensitive than standard EEG in patients with stroke, head injuries, and space-occupying lesions.[12,13] This sensitivity may be reflected in part by the increased number of electrodes, 28, compared with the standard 19-electrode EEG. The ability to color code amplitude and to average maps over time also increases sensitivity by identifying subtle changes that the human eye may not detect in a standard EEG format.

Ahn and colleagues[14] studied brain mapping during carotid endarterectomy in 46 patients. Overall, 63% of these patients received shunts. The decision to shunt was not based solely on the topographic map, although as the study progressed the surgeons came to rely more heavily on brain mapping. Preoperative brain maps were abnormal in 52% of their patients, compared with a 22% incidence of abnormalities with the use of standard EEG. With crossclamping, 50% of the patients had an ischemic change on the brain mapper, whereas only 28% had a change detected by standard EEG.

Ahn and associates[14] concluded that brain mapping is a sensitive tool that can detect subclinical ischemia or infarction. They believed that it was perhaps too sensitive, as 50% of patients had evidence of ischemia by brain mapping at the time of crossclamping. This is in distinction to our series, in which only 15% of the patients developed ischemia with crossclamping. This difference may be explained by the fact that in our series, changes classified as new ischemia required preexisting abnormalities to have a significant amplitude asymmetry that extended into an additional frequency band or that expanded in spatial distribution, whereas Ahn and associates[14] defined new ischemia based only on amplitude asymmetry criteria (Sheldon E. Jordan, MD, oral communication, January 1990).

The high incidence of abnormal preoperative brain maps in the subgroup of patients with TIAs has also been reported by Nagata and associates.[15] They studied patients with TIAs by means of a computerized mapping system and found an overall 68% incidence of EEG abnormalities in the preoperative state. In those patients tested within 2 weeks of the last TIA, the incidence of abnormal brain mapping increased to 88%. Ahn and associates[14] found a 67% incidence of preoperative abnormalities with brain mapping in those patients with TIAs. We think that many of these patients are admitted with recent or crescendo TIAs and that the brain mapper is able to detect subtle areas of focal perfusion defects that were previously unidentified by standard EEG.

Ischemic changes developed with crossclamping more often in patients with an abnormal preoperative map than those with a normal map ($P < .02$). This is not predictive of which patients will need a shunt, as only 23% of the patients with an abnormal preoperative map developed new ischemia with crossclamping. In our series, there was no correlation between a history of stroke and ischemic changes occurring at the time of crossclamping ($P = .50$). The preoperative map may correlate better with the need for shunting because of the high incidence of silent ischemia that the brain mapper can detect. Given these findings, it is reasonable to shunt not on the basis of an abnormal preoperative brain map image but rather on the basis of changes that occur at the time of crossclamping. Computerized topographic brain mapping is a sensitive, reliable, and readily interpretable means of monitoring cerebral perfusion during carotid surgery. We have come to rely on the computerized EEG data as the main criteria for selective shunting and for confirmation of shunt patency during carotid endarterectomy.

We would like to extend our appreciation to Maureen R. Whalen for her expertise in EEG monitoring and help in preparing the topographic brain maps for review.

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Discussion

RUDOLPH W. VOLLMAN, MD, Jamaica Plain, Mass: The type of neurologic monitoring for patients undergoing carotid endarterectomy remains controversial. The unreliability of stump pressure and jugular venous oxygen saturations, the cumbersomeness of xenon blood flow and intraoperative OPG, and the difficulty with technical challenges with the use of local anesthesia, especially in a teaching situation, have led most vascular surgeons to rely on the use of general anesthesia and selective intraluminal shunting for cerebral protection. Until now, the use of a standard 16-lead EEG with continuous intraoperative monitoring has been the benchmark for deciding in which patients to place a shunt for maintenance of cerebral perfusion during crossclamping.

This paper describes the use of a new computerized EEG topographic brain mapper that is a relatively simple, computer-based method for the computation and display of brain electrical activity. The advantages of this new technology are as follows: the brain mapping system collects data from 28 points on the skull rather than the 16 points of the standard EEG, and thus renders it more sensitive, with fewer gaps for determining brain ischemia. Second, the equipment is much smaller and more portable, and the image is displayed on a real-time screen and stored on a small computer disk rather than the reams of bulky paper of the EEG. Last, for the nonneurologists among us, the computer processing and display of brain activity in a color image is much easier to interpret in the operating room. The background activity and artifacts are muted, and the five EEG bands are amplified, averaged, and color coded.

Disadvantages to computerized topographic mapping also exist. The placement of 28 electrodes and maintaining their placement during endotracheal anesthesia is cumbersome and difficult to set up. The initial cost of the equipment is considerable. As the UCLA vascular group suggested, and as was corroborated by this paper, the system may be oversensitive to minor changes. More importantly, this paper emphasizes the ongoing need for accurate preoperative assessment of patients undergoing carotid endarterectomy. Dr Elmore and his colleagues have shown that more than 80% of patients with TIAs had abnormal scans (higher than the rate among the patients with stroke), which may represent crescendo TIAs or ongoing *silent* or subtle defects that are unidentified by the standard EEG. This is much greater than the *silent* cerebral infarction rate of 18% seen on radiologic computed tomographic scan that we described before this society 5 years ago (*Am J Surg*. 1984;147:492-497). As a corollary, they have shown that an abnormal preoperative computerized topographic map was a marker for the need of a shunt in 23% of their patients, but no patients with a normal preoperative computed tomographic scan required a shunt.

This leads me to several questions for the authors:

1. If the significance of abnormal computerized topographic scans in preoperative patients with TIAs is related to ongoing perfusion defects, presumably due to a tight stenosis or multiple emboli, why did 83% of their maps remain unchanged after the lesion was removed?

2. Is brain mapping too sensitive? In their series, it suggested shunting in only 15% of patients, but in the UCLA series it was over 50%. Will we place shunts in too many patients on the basis of this assessment?

3. If a preoperative computed tomographic scan were normal, would the authors perform the operation without this monitor, since none of the 22 patients who had a normal scan in their series developed ischemia, nor did they require a shunt?

4. Did the authors detect any nonfunctioning shunts during surgery by this method, since this was one of their indications for using the topographic mapping?

5. In this age of cost containment, how much do they think that the use of this new computer technology will increase the cost of carotid endarterectomy?

MAGRUDER C. DONALDSON, MD, Boston, Mass: We have had some experience at Brigham and Women's Hospital, Boston, with similar technology that processes the raw EEG to detect changes more accurately. We have found in about 140 patients that there is a 22% shunt rate, with a higher proportion in people with contralateral disease, particularly contralateral occlusion. Our philosophy has been that the head is to some extent a black box, with events that occur at a cellular level that are likely of great importance. If we can monitor these events during clamping, somewhere along the line it is likely to benefit the patient. We have used EEG routinely for many years and have evolved into this new computerized technology, which is really quite spectacular.

The issue of whether modern EEG is too sensitive has been a source of discussion in our group. There is clearly silent cerebral ischemia, as there is in the heart. Computed tomographic evidence has shown a significant incidence of scars in patients who have no symptoms to go with those scars. The EEG evidence is similarly impressive. It would be very interesting to combine EEG and computed tomographic findings with sophisticated clinical information obtained through cognitive or psychometric testing, following up a series of patients through carotid artery surgery with parallel sets of data. I wonder if Dr Elmore and his team have considered such a study.

Finally, there used to be a debate about selecting people for shunts. I wonder as we develop more and more sensitive indexes of what is happening in the cortex whether the debate will become in whom are we *not* going to place shunts. Perhaps it would be simpler and certainly cheaper not to measure anything, but to place shunts in everybody. Did Dr Elmore and his colleagues find any evidence with this new sensitive method that shunting is harmful?

DR ELMORE: Why are the vast majority of the maps unchanged in the postoperative period? We did find that 11% of the maps were improved and 83% unchanged. If you followed up these patients further you would find that more of these maps are improving. There were four patients who had maps that were worse postoperatively. We hypothesize that these changes were due to small microemboli that occur during the time of surgery, but we are not sure what they represent. None of these patients had a neurologic deficit. Of the patients who had normal preoperative maps, none developed ischemia with crossclamping. That is not enough to stop monitoring patients who have a normal preoperative brain map, but this warrants further investigation.

We used the mapper to confirm shunt patency in the 10 patients with shunts. The brain maps continued to show improvement in all patients with shunts in place. None of the brain maps worsened while the shunt was in place. During shunt removal, some surgeons totally occlude the artery, and, just in that minute period while the artery is occluded, we could actually see the maps turning blue again. We believe that brain mapping is adequate for confirmation of shunt patency.

Cost containment is always an issue with new technology. The machine costs approximately $100 000. We charge a total of $425 per patient for the preoperative, intraoperative, and postoperative monitoring and the neurologist's review of the maps. If we can prevent even one major stroke, the machine will quickly pay for itself.

To answer Dr Donaldson's question, there might be some harm from a shunt. Of the 10 patients in whom we placed shunts, 1 patient actually had a transient neurologic deficit that resolved before discharge. We wonder if this was due to an embolic event from the shunt. People have reported an approximate 0.5% incidence of emboli from shunting, and I therefore think it is a reasonable approach to be a selective shunter.

Is this technique too sensitive? Studies done by routine nonshunters with general anesthesia have found an approximate 2% stroke rate. Surgeons who use local anesthesia have reported a 9% incidence of neurologic changes at the time of crossclamping, and EEG studies have shown a 10% to 15% incidence of ischemic changes with crossclamping. In our hands, the brain mapper compares favorably with standard EEG in that we identified ischemia in 15% of the patients with crossclamping.

Albumin Supplementation in the Critically Ill

A Prospective, Randomized Trial

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• Albumin replacement to correct hypoalbuminemia in critically ill patients has been controversial. This study was a prospective, randomized trial of 25% albumin administration in 40 hypoalbuminemic (serum albumin, <25 g/L [2.5 g/dL]), critically ill patients. The treatment group (18 patients) received 25% albumin supplementation to achieve and maintain serum albumin levels of 25 g/L (2.5 g/dL) or greater, while the nontreatment group (22 patients) received no concentrated albumin. There was no clinical benefit from albumin therapy when assessing mortality (39% vs 27%, treatment vs control) or major complication rate (89% vs 77% of patients). There were also no significant differences in length of hospital stay, intensive care unit stay, ventilator dependence, or tolerance of enteral feeding, despite significant elevations of albumin in the treatment group. The costly use of exogenous albumin as treatment for hypoalbuminemia in this patient population does not appear to be justified.

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Hypoalbuminemia has been shown to be an accurate prognostic indicator of poor patient outcome in a wide variety of clinical settings. Warnold and Lundholm[1] in 1984 documented an increased complication rate and increased length of stay following surgery in patients with hypoalbuminemia preoperatively. Anderson and Wochos[2] confirmed an increased length of stay among a cohort of medical patients who were hypoalbuminemic on admission when compared with a similar group with normal serum albumin levels. More specifically, hypoalbuminemia has been associated with a variety of organ system dysfunctions, including pulmonary fluid overload,[3] enteral feeding intolerance,[4,5] and poor wound healing.[6] This correlation is based at least partially on the accuracy of hypoalbuminemia as a marker for serious disease processes, including sepsis[7] and malnutrition.[8] Theoretically, hypoalbuminemia itself may further contribute to morbidity by altering albumin's physiologic role in maintaining intravascular oncotic pressure, adversely affecting water balance between the intravascular and interstitial spaces.[9] Recent work has also suggested that albumin may have important roles as a scavenger of free radicals, a binding agent for toxic compounds in disease states, and a carrier for a wide variety of drugs and hormones.[10]

An increasing awareness of these physiologic functions of albumin and the direct association between hypoalbuminemia and morbidity has resulted in widespread use of albumin replacement therapy to restore normal albumin levels in hypoalbuminemic patients. In 1986, Hardin et al[11] showed conclusively that low serum albumin concentrations could be safely and rapidly restored with human albumin infusions. However, there are no conclusive data from prospective, randomized trials that this iatrogenic elevation in serum albumin concentrations reduces the high morbidity associated with hypoalbuminemia. Without this conclusive evidence, the high cost of human albumin administration has made its use as treatment for hypoalbuminemia controversial. This study is a prospective, randomized trial designed to assess the benefits of concentrated human albumin administration in critically ill, hypoalbuminemic patients receiving total parenteral nutrition.

PATIENTS AND METHODS

All patients referred to the New England Deaconess Hospital Nutrition Support Service, Boston, Mass, for nutritional assessment and total parenteral nutrition with serum albumin concentrations below 25 g/L (2.5 g/dL) were considered for entry. Potential subjects with Child's class C cirrhosis[12] were excluded. Forty patients were identified and entered into the study between August 1988 and April 1989. These patients were randomly assigned to either a treatment or nontreatment group by medical record number. The treatment group (18 patients) received 25 to 50 g/d of 25% albumin in addition to full nutritional support with parenteral nutrition. Albumin administration was continued daily until serum albumin levels exceeded 25 g/L (2.5 g/dL), after which patients received additional albumin as needed to keep the albumin level at 25 g/L (2.5 g/dL) or higher. Albumin was administered either continuously by adding the 25% solution directly to the patient's total parenteral nutrition, or by separate intravenous boluses three to four times per day. Intermittent bolus therapy was conducted when the patient was receiving total parenteral nutrition as a 3-in-1 admixture, with which human albumin solutions are incompatible. The nontreatment group (22 patients) received no exogenous concentrated albumin.

At the time of study entrance, thorough evaluations were conducted for all patients, which included general demographic data, medical histories, routine laboratory data, and a severity of illness score calculated by the APACHE (*a*cute *p*hysiology and *c*hronic *h*ealth *e*valuation) II scoring system.[13] All patients were fully evaluated by the Nutrition Support Service, and energy and protein needs were estimated (105 to 147 J/kg per day and 1.5 g of protein per kilogram per day) and provided. All patients initially were fed completely intravenously, but transition to enteral feedings was actively promoted by the Nutrition Support Service when clinically indicated. Patients were evaluated daily by the primary investigator, who collected all data.

Mortality, major complication rates, hospital stay, intensive care unit (ICU) stay, length of ventilator dependence, and tolerance of enteral feedings were tabulated. Complications were defined at the outset of the study, similar to prior definitions.[14,15] Cardiovascular complications included myocardial infarction (persistent electrocardiographic changes and isoenzyme elevations), major arrhythmias causing hemodynamic instability and requiring emergent antiarrhythmia therapy, cardiogenic shock (hypotension and hypoperfusion requiring vasopressor therapy), and deep venous thrombosis documented by venography. Pulmonary complications included pneumonia (chest roentgenographic changes and positive sputum cultures), pulmonary insufficiency requiring mechanical ventilation for greater than 24 hours, pneumothorax requiring chest tube placement, and pulmonary embolism documented by arteriography. Renal complications included acute renal failure requiring dialysis. Infectious complications consisted of all viral, bacterial, or fungal infections documented by cultures requiring systemic antimicrobial therapy. Gastrointestinal complications included bowel obstruction requiring surgical exploration, gastrointestinal bleeding documented by endoscopy and requiring transfusion of more than 3 U of packed red blood cells, and acute cholecystitis diagnosed clinically and treated with surgery or antibiotic therapy. Intra-abdominal sepsis was defined as a purulent collection drained either surgically or radiographically. A

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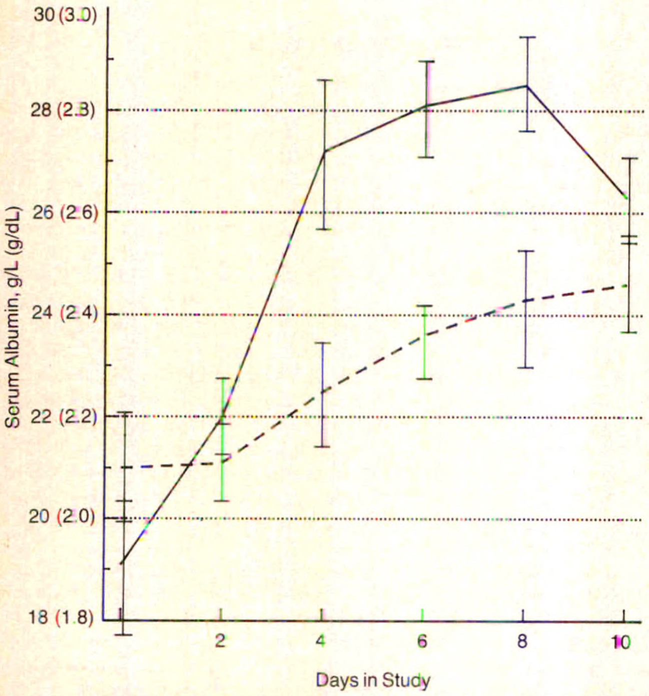
Table 1.—Patient Characteristics at Study Entry*

	Treatment	No Treatment
Age, y	63.2±4.2	66.4±3.4
Sex, % M	55	68
ICU, % (No.)	83 (15/18)	82 (18/22)
Ventilator dependent, % (No.)	72 (13/18)	59 (13/22)
Entry albumin, g/L (g/dL)	19±1 (1.9±0.1)	21±1 (2.1±0.1)
Entry APACHE score	18.4±2.3	18.0±1.7

*ICU indicates intensive care unit; APACHE, acute physiology and chronic health evaluation scoring system.[13] Values for age, albumin level, and APACHE score are means±SEMs. No difference is significant.



Mean (±SEM) serum albumin concentrations in the treatment (solid line) and nontreatment (broken line) groups over the first 10 days of study.

wound dehiscence required surgical closure. Fistulas were demonstrated radiographically, and wound infections required wound opening and drainage of purulent material.

All patients were followed up until discharge or death, with the exception of two patients (one in each group) who remained hospitalized at the study closure. Both of these patients had been hospitalized and actively enrolled in the study for greater than 2 months at the study closure.

Data were analyzed by the unpaired Student's *t* test, χ^2 analysis, or Wilcoxon tests where appropriate.[16] We considered $P<.05$ significant. All mean values are expressed as mean ± SEM unless otherwise noted. Patients were entered into the study under the guidelines of the Institutional Review Board for Human Studies at the New England Deaconess Hospital.

RESULTS

Eighteen patients were randomized to the treatment group and 22 to the nontreatment group. Two patients in the nontreatment group became profoundly hypoalbuminemic (<15 g/L [<1.5 g/dL]), and at the direction of the primary care team were treated with albumin, establishing a small crossover group. The crossover patients remained in the nontreatment group for statistical analysis. The characteristics of the treatment and nontreatment groups at entrance are outlined in Table 1. There were no significant differences in sex, age, percentage in the ICU, percentage who were ventilator dependent, serum albumin concentrations, or APACHE II scores at the time of study entrance. Ninety-three percent of patients were on the surgical services.

Table 2.—Mortality and Complications*

	Treatment	No Treatment
Mortality, No. (%)	7/18 (38.9)	6/22 (27)
Major complications Total No.	40	33
Patients, No. (%)	16/18 (89)	17/22 (77.3)
Complications per patient, mean±SEM	2.2±0.6	1.5±0.4

*No difference is significant.

The treatment group received a mean of 250.3±36.8 g of albumin per patient during the trial. The mean number of days required to achieve an albumin concentration of 25 g/L (2.5 g/dL) or greater was significantly shorter in the treatment group (4.2±0.5 vs 9.0±1.6 days; $P<.01$). The Figure depicts the mean serum albumin concentrations of the treatment and nontreatment groups from entrance to day 10 of the study. As shown, the mean serum albumin concentrations were significantly higher in the treatment group by day 4 and remained significantly higher until day 10 of the study. After this, there were no significant differences in albumin levels between the groups, primarily because the nontreatment group's mean albumin levels approached the treatment limit of 25 g/L (2.5 g/dL) by day 10.

Despite the significant differences in albumin levels between the groups early in the study, we found no significant differences in overall mortality or major complication rate (Table 2). The high mortality and complication rates underscore the severity of illness of this patient population. A breakdown of major complications is given in Table 3. Consistent with this lack of altered morbidity or mortality, there were no significant differences in total hospital days or ICU days following entrance into the study. Furthermore, there were no significant differences in the number of days of ventilator dependence or the length of time required before the patient was able to tolerate 70% or greater of energy needs enterally (Table 4). In addition, when including only the first 10 days of study when serum albumin concentrations were significantly higher in the treatment group, there were still no improvements in length of ICU stay (7.2±1.7 vs 5.3±0.3 days; not significant, treatment vs control) or ventilator dependence (6.0±1.0 vs 3.8±1.3 days; not significant).

The cost of albumin therapy in the treatment group was substantial. A total of 4505 g of albumin was administered, costing approximately $18 000, or roughly $1000 per patient.

COMMENT

Our data suggest that albumin therapy for the treatment of hypoalbuminemia in critically ill patients, despite its demonstrated value in raising the serum albumin concentration, has no beneficial impact on a variety of outcome variables, including mortality, complication rate, hospital stay, ventilator dependence, or tolerance of enteral feeding. Despite the association of hypoalbuminemia and high morbidity, the inability of iatrogenic elevation of the serum albumin concentration to reverse that high morbidity suggests the lack of a causal relationship. Hypoalbuminemia often results from a combination of acute and chronic disease processes, including liver dysfunction, malnutrition, and sepsis.[7,8,17] Aggressive therapy

Table 3.—Complications

Complication Type	Therapy	No Therapy
Cardiovascular		
Major arrhythmia	1	0
Myocardial infarction	1	4
Deep vein thrombosis	0	2
Shock	0	2
Stroke	0	1
Pulmonary		
Pneumonia	3	2
Pneumothorax	1	0
Respiratory failure	2	1
Gastrointestinal		
Cholecystitis	2	0
Bleeding	3	1
Small-bowel obstruction	1	0
Acute renal failure	4	2
Infectious		

lights the transitory impact of albumin supplementation on serum albumin levels due to the redistribution of albumin from the intravascular to extravascular spaces. Our data document the rapidity of this redistribution, particularly in critically ill patients, where sepsis often increases capillary wall permeability. In conjunction with the slow but steady improvement of serum albumin levels in the nontreatment group, this redistribution contributes to the relatively short-term impact of even aggressive albumin replacement to elevate serum albumin concentrations and subsequently may limit its effectiveness in improving clinical outcome.

Two recent studies have suggested advantages of albumin replacement therapy in hypoalbuminemic patients. Brown et al,[18] in a study of similar design done in 1988, documented a greater than twofold decrease in major complications in a group of hypoalbuminemic patients treated with exogenous human albumin solutions. However, despite a greater than twofold reduction in complications, these investigators did not observe any significant reduction in length of hospital stay or mortality. When an apparent reduction in complications is unassociated by any change in mortality or length of stay, the

[redacted]

better outcome. By the sign test, this would be unlikely (1 in 64 chances or $P<.02$) if there was no true difference between the groups, and even more unlikely if the treatment group truly benefited from therapy. Viewed in another way were the trends in mortality to continue, at a sample size of 136 the results would show significantly poorer survival in the treatment group ($\alpha=.05$ and $\beta=.02$). These points suggest that at the least it is very unlikely that benefit from treatment would be seen if the study groups were expanded. Although no significant differences were documented, the trend of poorer outcome in the treatment group suggests that population expansion may even document significant morbidity from albumin therapy.

The substantial cost of human albumin, particularly at a time of growing concern over cost containment, dictates that the controversy over the efficacy of albumin therapy be resolved. In our small patient group alone, patients received approximately $1000 per patient worth of albumin solutions with no demonstrable benefit. As the data of Ford et al suggest, there may be some specific indications in some selected patients where this therapy may be beneficial, but in our experience, the use of concentrated albumin solutions as general therapy for hypoalbuminemia in conjunction with total parenteral nutrition in critically ill patients does not appear to be justified.

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Discussion

ROCCO ORLANDO III, MD, Hartford, Conn: It is important that we subject high-cost interventions in the ICU to prospective evaluation, even where there is a well-established theoretical basis for that therapy. In our institution, we currently spend over $300 000 a year on albumin, and it is appropriate that we look prospectively at this kind of question.

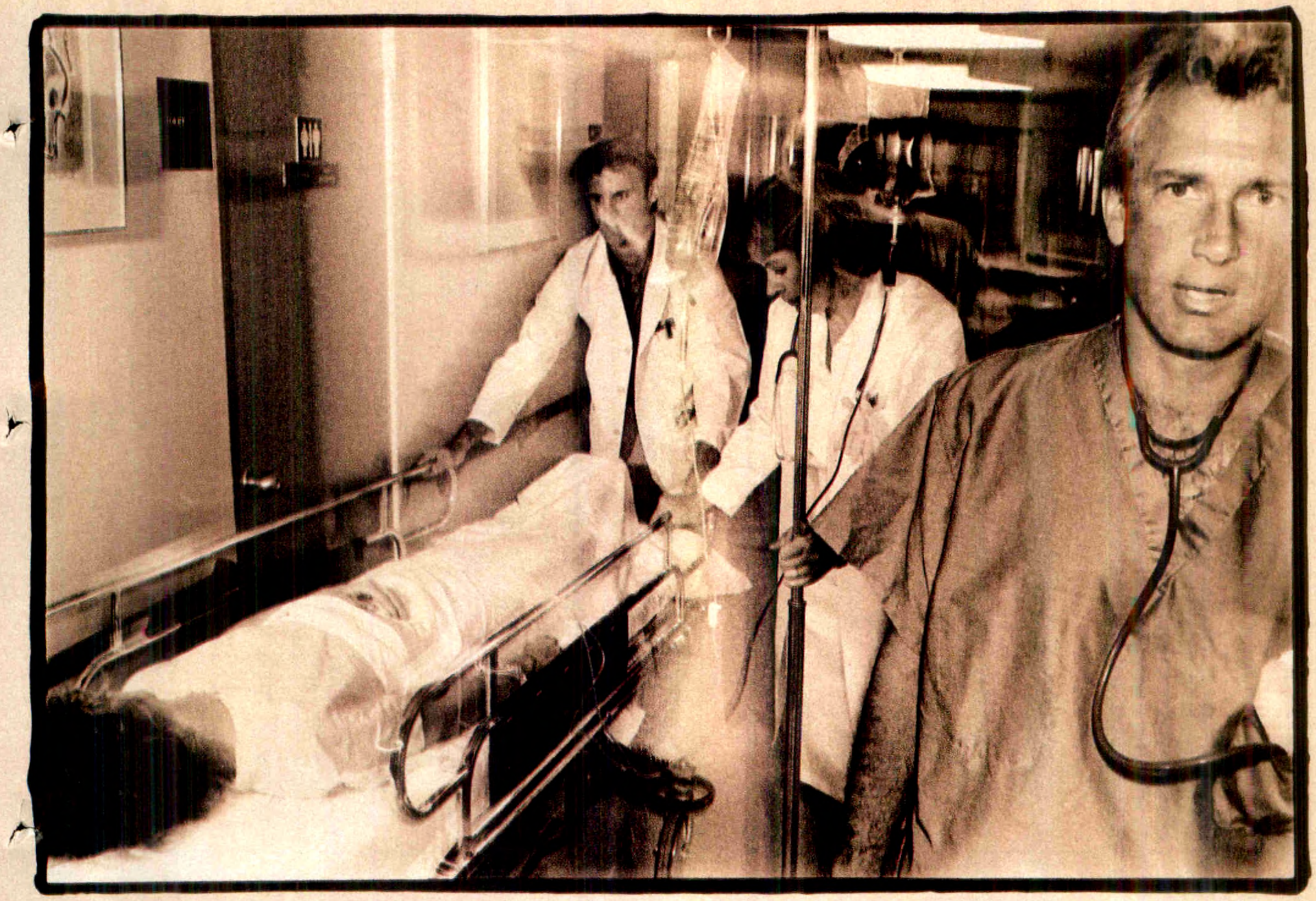
Like most critical care investigators, the authors have raised issues that bear on the first two laws of critical care. The first law of critical care is that sick people die more often than healthy people, and that is well documented in this study. They had a high severity of illness, with high APACHE scores. Given the high acuity, is it reasonable to expect that we would see a change in an end point as crude as mortality? I would also ask the authors if they gave enough albumin. There are those zealous users of albumin who would suggest that although there was a statistically significant increase in the serum albumin level, the mean serum albumin value was still on the order of 28 to 30 g/L after the treatment period. Had they pushed it higher, might they perhaps have seen an impact of albumin therapy?

The third question relates to tolerance of tube feedings. It has been accepted that patients with low serum albumin levels are intolerant of tube feedings, and it has been suggested again with little documentation that exogenous serum albumin will improve tolerance to enteral feeding. How did the authors define intolerance of tube feedings? Might they have had a different result if they had looked at this question in patients who had fewer gastrointestinal and abdominal surgical complications? There was a fairly high rate of abdominal surgical complications and illnesses, and in a group of patients with malnutrition with low serum albumin levels, they might have achieved a different result.

The second law of critical care is that you do not have to understand it to treat it. The authors are clearly trying to repeal this second law and are to be commended for bringing this very important and useful report to our attention.

DR FOLEY: In regard to our findings about the tolerance of enteral feedings, I think that Dr Orlando's point is well taken. There are many reasons in the ICU setting among critically ill patients, particularly patients who have a multitude of intra-abdominal surgeries and complications, for the intolerance of tube feedings. In this particularly ill group of patients, there were many episodes of hemodynamic instability, multiple antibiotic regimens, and a variety of other organ system dysfunctions that may have contributed to the lack of tolerance of enteral feedings beyond the impact that low serum albumin concentration may have made alone. There is one prospective study, by Ford et al,[19] published about 2 years ago, that was done on a group of pediatric patients who were much less sick than the patients whom we studied. In this group of hypoalbuminemic pediatric patients who were not tolerating tube feedings, they found that albumin supplementation improved these patients' tolerance of feedings. The researchers had the advantage in their patient population, I think, of ruling out many of these other causes of feeding intolerance that may have influenced the findings in our patients. I agree that our findings about tolerance of tube feedings can not be extrapolated to all types of patients, but we do stand by our conclusion that increasing albumin levels does not seem to improve feeding tolerance in patient populations such as ours.

The second question that Dr Orlando brought up is, did we give enough albumin? The theoretical basis of the benefits of albumin administration lies in its improvement or restoration of the physiologic functions of albumin. We thought that the greatest potential impact of albumin therapy would be in improving severely low albumin levels, which our protocol successfully accomplished. Because we did not see even any suggestion of benefit in our treatment group in this range of albumin concentration improvement, I doubt that further improvement of albumin levels from mildly depressed to normal would radically alter our findings. Furthermore, more aggressive albumin supplementation would substantially increase the already high cost of such therapy.



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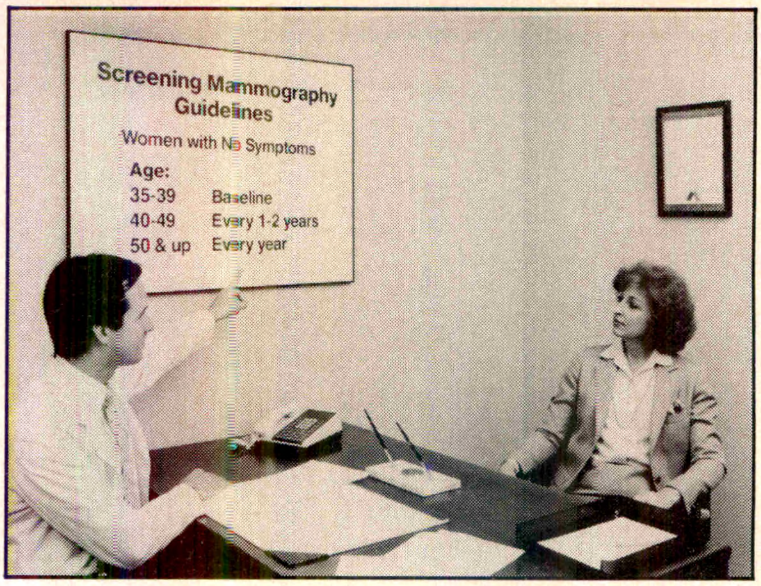

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INDICATIONS AND USAGE

UNASYN is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.

Skin and Skin Structure Infections caused by beta-lactamase producing strains of *Staphylococcus aureus*, *Escherichia coli*,* *Klebsiella* spp.* (including *K. pneumoniae**), *Proteus mirabilis*,* *Bacteroides fragilis*,* *Enterobacter* spp.,* and *Acinetobacter calcoaceticus*.*

Intra-Abdominal Infections caused by beta-lactamase producing strains of *Escherichia coli*, *Klebsiella* spp. (including *K. pneumoniae**), *Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.*

Gynecological Infections caused by beta-lactamase producing strains of *Escherichia coli*,* and *Bacteroides* spp.* (including *B. fragilis**).

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

While UNASYN* (ampicillin sodium/sulbactam sodium) is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.

CONTRAINDICATIONS

The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS

General: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN.

Drug/Laboratory Test Interactions: Administration of UNASYN will result in high urine concentrations of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriolglucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with UNASYN.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy

Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See—Drug/Laboratory Test Interactions.)

Labor and Delivery: Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.

Pediatric Use: The efficacy and safety of UNASYN have not been established in infants and children under the age of 12.

ADVERSE REACTIONS

UNASYN is generally well tolerated. The following adverse reactions have been reported.

Local Adverse Reactions

Pain at IM injection site—16%
Pain at IV injection site—3%
Thrombophlebitis—3%

Systemic Adverse Reactions

The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.

Additional systemic reactions reported in less than 1% of the patients were itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis and mucosal bleeding.

Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

Hepatic: Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.

Hematologic: Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.

Blood Chemistry: Decreased serum albumin and total proteins.

Renal: Increased BUN and creatinine.

Urinalysis: Presence of RBC's and hyaline casts in urine.

The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN.

Gastrointestinal: Gastritis, stomatitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity Reactions: Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin (see WARNINGS).

Hematologic: In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

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(ampicillin sodium/sulbactam sodium)

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INDICATIONS AND USAGE

UNASYN is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.

Skin and Skin Structure Infections caused by beta-lactamase producing strains of *Staphylococcus aureus*, *Escherichia coli*,* *Klebsiella* spp.* (including *K. pneumoniae**), *Proteus mirabilis*,* *Bacteroides fragilis*,* *Enterobacter* spp.,* and *Acinetobacter calcoaceticus*.*

Intra-Abdominal Infections caused by beta-lactamase producing strains of *Escherichia coli*, *Klebsiella* spp. (including *K. pneumoniae**), *Bacteroides* spp. (including *B. fragilis*), and *Enterobacter* spp.*

Gynecological Infections caused by beta-lactamase producing strains of *Escherichia coli*,* and *Bacteroides* spp.* (including *B. fragilis**).

*Efficacy for this organism in this organ system was studied in fewer than 10 infections.

While UNASYN® (ampicillin sodium/sulbactam sodium) is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with UNASYN due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to UNASYN should not require the addition of another antibiotic.

CONTRAINDICATIONS

The use of UNASYN is contraindicated in individuals with a history of hypersensitivity reactions to any of the penicillins.

WARNINGS

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE APT TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR HYPERSENSITIVITY REACTIONS TO MULTIPLE ALLERGENS. THERE HAVE BEEN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE THERAPY WITH A PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, UNASYN SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

PRECAUTIONS

General: A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis. In patients treated with UNASYN the possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with UNASYN may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with UNASYN and allopurinol administered concurrently. UNASYN and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of UNASYN.

Drug/Laboratory Test Interactions: Administration of UNASYN will result in high urine concentrations of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™) be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriolglucuronide, conjugated estrone, and estradiol has been noted. This effect may also occur with UNASYN.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy

Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to UNASYN. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (See—Drug/Laboratory Test Interactions.)

Labor and Delivery: Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of UNASYN in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when UNASYN is administered to a nursing woman.

Pediatric Use: The efficacy and safety of UNASYN have not been established in infants and children under the age of 12.

ADVERSE REACTIONS

UNASYN is generally well tolerated. The following adverse reactions have been reported.

Local Adverse Reactions

Pain at IM injection site—16%
Pain at IV injection site—3%
Thrombophlebitis—3%

Systemic Adverse Reactions

The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.

Additional systemic reactions reported in less than 1% of the patients were: itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis and mucosal bleeding.

Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

Hepatic: Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH.
Hematologic: Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets.
Blood Chemistry: Decreased serum albumin and total proteins.
Renal: Increased BUN and creatinine.
Urinalysis: Presence of RBC's and hyaline casts in urine.

The following adverse reactions have been reported with ampicillin-class antibiotics and can also occur with UNASYN.

Gastrointestinal: Gastritis, stomatitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis.

Hypersensitivity Reactions: Urticaria, erythema multiforme, and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with a penicillin (see WARNINGS).

Hematologic: In addition to the adverse laboratory changes listed above for UNASYN, agranulocytosis has been reported during therapy with penicillins. All of these reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena.

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Lower antibiotic costs without lowering your standards. UNASYN costs at least 40% less per day than clindamycin/gentamicin or cefoxitin.[11] Yet UNASYN is at least as effective in a variety of mixed infections.*[3,12-19]

And in some studies versus combination therapy, patients treated with UNASYN spent fewer days in the hospital.[3,16,17]

So, look to UNASYN for highly effective, highly affordable therapy in mixed infections* every day.

1.5 or 3g q6h

Unasyn® IM IV

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Please see brief summary of prescribing information on adjacent page.

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TABLETS
Pepcid®
(Famotidine|MSD)
20 mg and 40 mg

ORAL SUSPENSION
Pepcid®
(Famotidine for Oral Suspension|MSD)
40 mg per 5 mL

INJECTION
Pepcid® IV
(Famotidine|MSD)
20 mg per 2 mL

Contraindications: Hypersensitivity to any component of these products.

Precautions: ***General:*** Symptomatic response to therapy does not preclude the presence of gastric malignancy.

Patients with Severe Renal Insufficiency: Longer intervals between doses or lower doses may be needed in patients with severe renal insufficiency (creatinine clearance <10 mL/min) to adjust for the longer elimination half-life of famotidine (see Clinical Pharmacology and Dosage and Administration sections of Prescribing Information).

Information for Patients: The oral suspension should be shaken vigorously for 5 to 10 seconds prior to each use, and unused constituted oral suspension should be discarded after 30 days.

Drug Interactions: No drug interactions have been identified. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine, and antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In rats and mice given oral doses up to approximately 2,500 times the recommended human dose for active duodenal ulcer, there was no evidence of carcinogenic potential; at these doses in rats, fertility and reproductive performance were not affected. No evidence of a mutagenic effect was observed.

Pregnancy: *Pregnancy Category B*—There are no adequate or well-controlled studies in pregnant women. Use during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether famotidine is secreted into human milk; however, it is secreted into the milk of lactating rats. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: No dosage adjustment is required based on age but may be necessary in severe renal impairment (see Clinical Pharmacology section of Prescribing Information).

Adverse Reactions: The adverse reactions listed below have been reported during domestic and international clinical trials in approximately 2,500 patients. In the placebo-controlled clinical trials, the incidence of adverse experiences with PEPCID Tablets 40 mg at bedtime was similar to that with placebo.

Incidence Greater than 1%: The following adverse reactions have been reported to occur in more than 1% of patients on therapy with PEPCID in controlled clinical trials and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%), and diarrhea (1.7%).

Causal Relationship Unknown: The following other adverse reactions have been reported infrequently and within each category are listed in order of decreasing severity. The relationship to therapy with PEPCID has been unclear in many cases. *Body as a Whole*—Fever, asthenia, fatigue. *Cardiovascular*—Palpitation. *Gastrointestinal*—Cholestatic jaundice, liver enzyme abnormalities, vomiting, nausea, abdominal discomfort, anorexia, dry mouth. *Hematologic*—Pancytopenia, leukopenia, thrombocytopenia. *Hypersensitivity*—Anaphylaxis, angioedema, orbital or facial edema, urticaria, rash, conjunctival injection. *Musculoskeletal*—Musculoskeletal pain, arthralgia. *Nervous System/Psychiatric*—Grand mal seizure; reversible psychic disturbances including hallucinations, confusion, agitation, depression, anxiety, decreased libido; paresthesia; insomnia; somnolence. *Respiratory*—Bronchospasm. *Skin*—Alopecia, acne, pruritus, dry skin, flushing. *Special Senses*—Tinnitus, taste disorder.

The adverse reactions reported for PEPCID Tablets may also occur with PEPCID Oral Suspension or PEPCID I.V.; in addition, transient irritation at the injection site has been observed with PEPCID I.V.

AV block has been reported with other H_2-receptor antagonists, but not with famotidine.

Management of Overdosage: There is no experience to date with deliberate overdosage. Up to 640 mg/day have been given to patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

Dosage and Administration: ***Duodenal Ulcer:*** The recommended adult oral dosage for active duodenal ulcer is 40 mg h.s.; most patients heal within 4 weeks, and it is rarely necessary to use the full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective. For maintenance therapy, the recommended oral dosage is 20 mg h.s.

Benign Gastric Ulcer: The recommended adult oral dosage for active benign gastric ulcer is 40 mg h.s.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas): The dosage varies with the individual patient; the recommended adult oral starting dosage is 20 mg q6h, but some patients may require a higher starting dosage. Dosages should be adjusted to individual patient needs and continued as long as clinically indicated; up to 160 mg q6h have been administered to some patients with severe Zollinger-Ellison syndrome.

Oral Suspension: The oral suspension may be substituted for tablets.

Directions for Preparing PEPCID Oral Suspension: Prepare suspension at time of dispensing. Slowly add 46 mL Purified Water. Shake vigorously for 5 to 10 seconds immediately after adding the water and immediately before use.

Stability of PEPCID Oral Suspension: Unused constituted oral suspension should be discarded after 30 days.

Intravenous Administration: In some hospitalized patients with pathological hypersecretory conditions or intractable ulcers or in patients who are unable to take oral medication, the recommended intravenous dosage is 20 mg q12h. For preparation of intravenous solutions for injection or infusion and for compatible diluents, please see Prescribing Information. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Concomitant Use of Antacids: Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Severe Renal Insufficiency: In patients with severe renal insufficiency (creatinine clearance less than 10 mL/min), the elimination half-life of famotidine may exceed 20 hours, reaching approximately 24 hours in anuric patients. Although no relationship of adverse effects to high plasma levels has been established, to avoid excess accumulation of the drug, the dosage may be reduced to 20 mg h.s. or the dosing interval may be prolonged to 36 to 48 hours as indicated by the patient's clinical response.

How Supplied: Tablets, containing 20 mg or 40 mg famotidine, with hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide as inactive ingredients, in unit-of-use bottles of 30 and 100 and unit-dose packages of 100; Oral Suspension, containing 40 mg famotidine per 5 mL after constitution with 46 mL Purified Water, with citric acid, flavors, microcrystalline cellulose and carboxymethylcellulose sodium, sucrose, and xanthan gum as inactive ingredients, and sodium benzoate 0.1%, sodium methylparaben 0.1%, and sodium propylparaben 0.02% added as preservatives, in bottles of 400 mg famotidine for constitution; Solution for intravenous injection, containing 10 mg famotidine per mL, with L-aspartic acid 4 mg, mannitol 20 mg, and Water for Injection q.s. 1 mL as inactive ingredients, and benzyl alcohol 0.9% added as preservative to the multidose vial, as 10x2-mL single-dose vials and as 4-mL vials.

For more detailed information, consult your MSD Representative or see Prescribing Information.
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New Angioscopic Findings in Graft Failure After Infrainguinal Bypass

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• We have previously shown that intraoperative angioscopy is a safe, useful, and effective method for monitoring infrainguinal bypass grafts. The videotaped recordings of the intraoperative angioscopy studies of 25 failed infrainguinal bypass grafts inserted between May 1987 and July 1989 and 3 failing grafts that were angioscoped during the subsequent graft salvage procedure were reviewed in a systematic fashion according to a fixed protocol, to identify any endovascular findings either initially missed or in which the relevance to graft failure had been unappreciated at the time of bypass grafting. We were able to identify new venous pathologic characteristics and highlight endoluminal features, of both a technical and nontechnical nature, which have a probable causal relationship to graft failure. However, the significance of some of the endovascular findings that were seen during infrainguinal bypass grafting has yet to be fully defined.

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Despite a large clinical experience with infrainguinal bypass grafting, including the use of intraoperative angiography, the causes and pathogenesis of both early (<30 days) and late (>30 days) graft failure often remain obscure. Currently, all methods used for monitoring infrainguinal bypass grafts intraoperatively are indirect. The intraoperative angiogram is the most frequently used method for monitoring these bypass grafts and, although highly specific, has only a moderate sensitivity.[1] Other indirect methods, such as electromagnetic flow metering, continuous-wave Doppler, ultrasound, or duplex scanning, for the intraoperative assessment of infrainguinal bypass grafts have limitations that have prevented their universal use.[2-4]

We have previously shown that intraoperative angioscopy, which allows a direct, in vivo, three-dimensional examination of the interior of the native vessels and grafts in real-life colors, is a safe, useful, and effective method for monitoring infrainguinal bypass grafts.[5] Not only does angioscopy allow the detection and immediate correction of technical defects during the grafting procedure, but it provides a method to identify and characterize new endovascular findings that are not available by other monitoring techniques. In the coronary arteries, angioscopy during coronary artery bypass surgery showed that the common clinical presentations of myocardial ischemia seem to have specific, identifiable intimal pathologic features.[6]

Some endovascular findings, such as residual competent valves or gross technical defects, are easily detected by angioscopy and can be seen to place a graft "at risk" of failure. However, many of the more subtle endoscopic findings that may be associated with graft failure, whether in the native arteries, the anastomosis, or the graft itself, have yet to be fully defined.

The purpose of this study was to review the previously videotaped angioscopic examinations performed at the time of graft insertion of all failed infrainguinal grafts, or at the time of graft salvage in failing infrainguinal bypass grafts, to describe these findings and attempt to relate these findings to graft failure.

PATIENTS AND METHODS

The videotaped recordings of the intraoperative angioscopy studies of all failed infrainguinal bypass grafts (25 grafts) inserted between May 1987 and July 1989 and failing grafts (3 grafts) that were angioscoped during the graft salvage procedure were reviewed in a systematic fashion according to a fixed protocol. The visual quality and completeness of the study were recorded. The distal artery was graded as to the severity of disease—minimal, moderate, or severe—taking into account the size of the lumen, the regularity of the intimal surface, and the presence of the protruding plaque. The anastomosis was observed systematically with particular attention to the size, shape, and patency of the apex of the anastomosis; the regularity of the suture lines, the hood, and arterial floor; the presence of thrombus, its volume and site, whether fresh or organized, whether red or white, with the latter being composed mostly of platelets; and the presence of intimal flaps, their size, degree of tethering, and luminal obstruction. For vein grafts, the luminal size, the vein quality with regard to the surface characteristics, such as sclerosis, presence of fresh or organized thrombus, localized injury, the number of valves and their configuration, and any other abnormalities, was noted. For the in situ and nonreversed bypasses, the number of valves and whether they had been rendered incompetent, the number of unligated tributaries, and the presence of localized valvulotome-induced injury were recorded.

Angioscopy was performed in a routine, standardized fashion, with angioscopes of 0.8 to 3.0 mm in external diameter (Olympus Corp, Lake Success, NY) by a separate "angioscopy team." The techniques, methods, and results of intraoperative angioscopy performed during infrainguinal revascularization have been previously reported.[5,7]

RESULTS

Twenty-five grafts (11.5%) of 219 infrainguinal bypasses, including 164 infrapopliteal bypass grafts, performed and monitored by angioscopy during the study period subse-

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Read before the 70th Annual Meeting of the New England Surgical Society, Bretton Woods, NH, September 24, 1989.

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Table 1.—Angioscopic Findings in Failed Infrainguinal Bypass Grafts*

Patient Graft No./Sex/Age, y	Bypass	Failure†	Angioscopic Findings		Comment
			At Initial Bypass Operation	At Reoperation/Thrombectomy	
			Early Graft Failure Group		
1/F/74	FEM-POP RV	1	Small outflow artery containing fibrinous material	Not done	Poor runoff
2/M/47	FEM-POP PTFE	21	Severe distal artery occlusive disease	Severe occlusive disease of popliteal bifurcation	Poor runoff
3/F/74	FEM-AT ISV	1	Organized thrombus in distal artery	Organized thrombus in AT	Poor runoff
4/F/60	POP-DP	4	Grossly irregular anastomosis with small apex (<1.4 mm), localized valvulotome-induced injury	Not done	Poor runoff, flawed anastomosis
5/M/74	FEM-PT ISV	1	Small anastomotic apex, platelet thrombus of distal anastomosis	Not done	Poor runoff, flawed anastomosis
6/M/40	FEM-PT ISV	1	Intimal flap at distal anastomosis	Not done	Flawed anastomosis
7/M/66	FEM-POP NRV	2	Irregular anastomosis, residual competent valve	Residual competent valve leaflet	Poor conduit
8/M/93	FEM-PT	1	Sclerotic "webbed" vein	Not done	Poor conduit
9/F/68	Vein patch to FEM-POP graft ISV	7	Severe diffuse intimal hyperplasia, localized stenosis of vein graft	Not done	Poor conduit
10/M/80	FEM-PT ISV	6	Vein stenosis	Residual thrombus removed by embolectomy catheter	Poor conduit
11/F/59	FEM-PT ISV	3	Inability to pass angioscope	Not done	Incorrect tunneling
12/M/66	FEM-POP ISV	7	None	Not done	Improper tunneling
13/F/65	FEM-POP NRV	5	Graft torsion	Not done	Graft torsion
14/M/57	FEM-POP NRV	14	Angioscopic-guided thrombectomy of distal artery	Not done	Hypercoagulable state
15/M/65	FEM-PT composite	1	Irregular venovenous anastomosis, arterial inflow stenosis	Not done	Poor inflow
16/M/80	Graft-POP RV	7	Severe iliac stenosis, proximal anastomotic thrombus	Not done	Poor inflow
17/M/75	FEM-PT PTFE	14	None (incomplete angioscopic examination)	Not done	Unknown
18/M/65	POP-DP RV	1	None (incomplete angioscopic examination)	Not done	Unknown
19/M/59	FEM-AT	1	2 residual valves	Not done	Unknown
			Delayed Graft Failure Group		
20/M/65	FEM-AT RV	15	Severe distal arterial disease	Not done	Poor outflow
21/M/54	FEM-POP PTFE	4	Severe distal arterial disease	Not done	Poor outflow
22/M/59	FEM-AT ISV	4	Severe distal arterial disease, thrombus on distal anastomosis, valvulotome-induced injury	Not done	Poor outflow, flawed anastomosis, ? poor conduit
23/F/69	FEM-POP NRV	4	Large intimal flap at distal anastomosis	Not done	Flawed anastomosis
24/M/70	FEM-DP ISV	5	3 residual competent valve leaflets	Residual thrombus following urokinase	? Poor conduit
25/M/68	FEM-POP ISV	3	Valvulotomy-induced injury	Not done	? Poor conduit
			Failing Grafts		
26/M/80	FEM-POP RV	84	Distal artery "pinhole" stenosis, atheromatous degeneration of vein graft, proximal anastomotic stenosis and thrombus on hood of graft	Not done	Poor inflow, poor conduit, poor outflow
27/F/68	FEM-POP ISV	11	Intimal hyperplasia of graft, "blind" popliteal artery, 2 competent valve leaflets	Not done	Poor conduit, poor outflow
28/M/83	FEM-POP ISV	3	Multiple unligated tributaries	Not done	AV steal

*FEM-POP indicates femoropopliteal; RV, reversed vein graft; PTFE, polytef; AT, anterior tibial artery; ISV, in situ vein graft; DP, dorsalis pedis artery; PT, posterior tibial artery; NRV, nonreversed vein graft; and AV, arteriovenous.

†For "early" group, failure is given in days; for "delayed" group and "failing" grafts, failure is given in months.

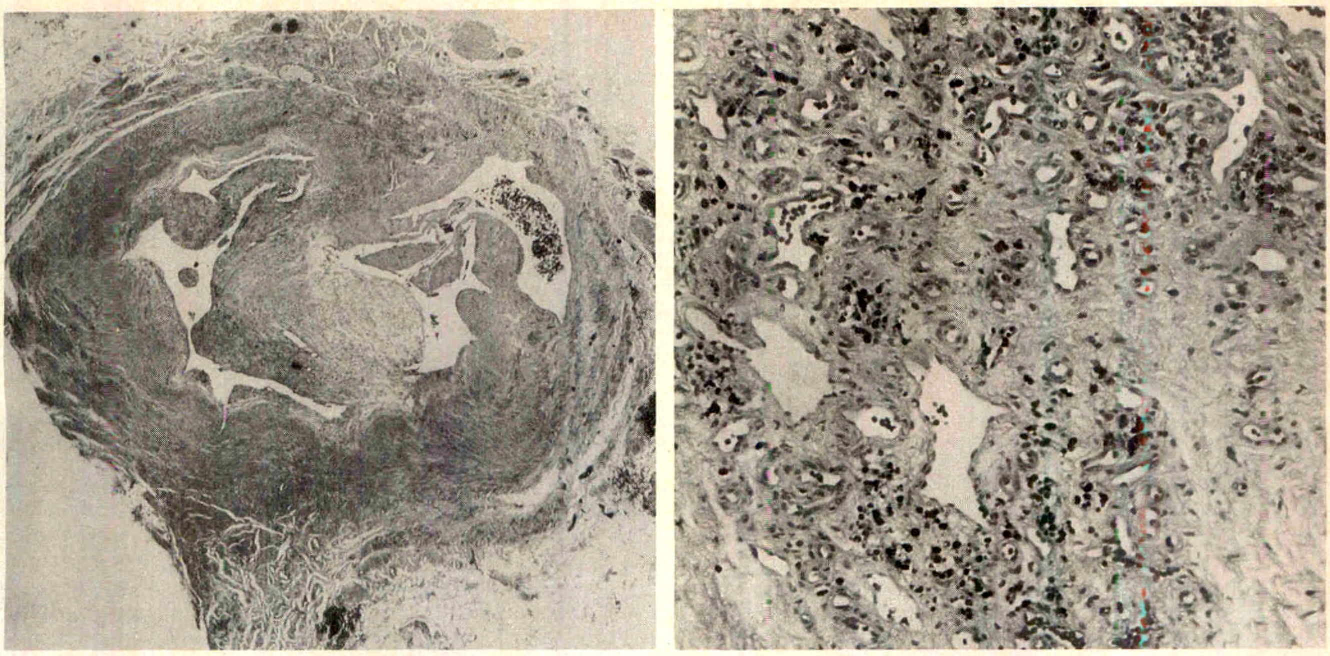


Fig 1.—Partially occluded saphenous vein due to recanalized organized thrombus. Left, Low-power photomicrograph of vein cross section demonstrates residual webs from recanalization of vessel. Right, High-power photomicrograph demonstrates neovascularization with both large and small blood channels, chronic inflammation, and hemosiderin pigment indicative of organized thrombus (hematoxylin-eosin, ×20 [left] and ×150 [right]).

quently occluded (Table 1, Nos. 1 through 28). Nineteen grafts (7.8%) failed within 30 days of operation, and 6 grafts (3%) failed after 3 months. A further 3 cases, operated on at different institutions and referred for further management, were diagnosed as failing grafts on clinical examination and noninvasive laboratory testing. Intraoperative angioscopy was performed as part of the salvage revascularization procedure for these failing grafts.

In only 4 of the 19 grafts that failed within 30 days and in 1 of the 6 grafts that failed between 3 and 15 months (Table 1) was intraoperative angioscopy performed during the reoperation. This was due to either logistic problems that made angioscopy unavailable or the primary surgeon's decision not to perform angioscopy.

The angioscopic findings of the failed and failing grafts were grouped into those associated with a compromised "runoff" in the distal artery, technical flaws of the anastomosis, factors influencing the vein graft quality, and diminished inflow problems (Table 1).

In the "early" graft failure group (Table 1, Nos. 1 through 19), grafts 1 through 3 showed severe atherosclerotic disease and stenosis of the distal artery. In grafts 4 through 6, there were problems with both the anastomosis and distal artery. Poor vein graft quality, including sclerotic and recanalized vein (Fig 1), vein stenosis, as well as improper tunneling and graft torsion, were seen on the angioscopic studies of grafts 7 through 13. Inadequate inflow was the reason for graft failure in grafts 15 and 16, but angioscopic examination of the inflow vessels was not performed in either of these grafts. Graft 14 occluded in a patient with carcinomatosis due to a hypercoagulable state, and in grafts 17 and 18, the angioscopic examination was incomplete. In case 19, "blind" retrograde valvulotomy of two residual competent valve leaflets, detected during the angioscopy, was performed, and the result was not reexamined with angioscopy.

In the "late" graft failure group (Table 1, Nos. 20 through 25), angioscopy showed severe distal outflow disease in grafts 20 through 22. In addition to a severely diseased distal artery, in graft 22, there were large volumes of fresh thrombus on the distal anastomosis and multiple areas of localized valvulotome-induced injury throughout the vein. In graft 23, a large, partially occluding intimal flap at the apex of the distal anastomosis was misinterpreted with regard to its significance. The anastomosis was not explored, and the intimal flap was not removed. In graft 24, multiple residual uncut competent valve leaflets were noted and cut during the angioscopy study. In graft 25, multiple regions of valvulotomy-induced injury was the only abnormality noted.

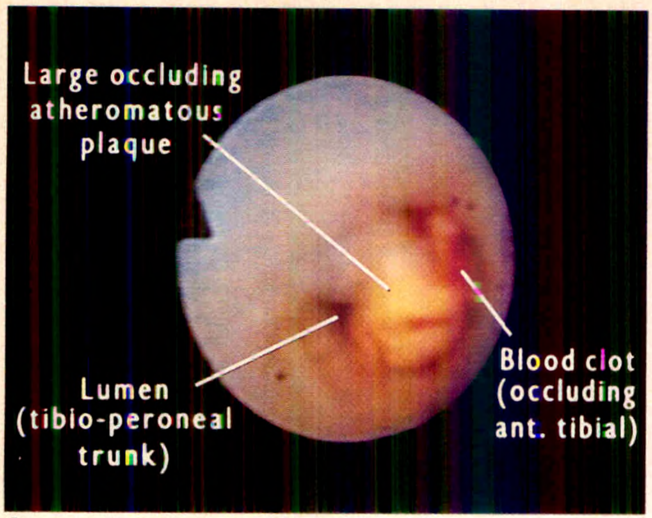
Three nonoccluded grafts (Table 1, Nos. 26 through 28), failing after 7 years and 11 and 3 months, respectively, were angioscoped during surgery for the graft salvage. Graft 26, after functioning for 7 years, had a "pinhole" stenosis just distal to the distal anastomosis, localized regions of atherosclerotic graft degeneration throughout the vein graft, and a severe proximal anastomotic stenosis. A distal jump graft was performed (Table 1, graft 16). Graft 27, after 11 months, showed long segments of severe intimal hyperplasia that caused severe graft stenosis just distal to the proximal anastomosis and in the middle segment of the vein graft. Other angioscopic findings included two flimsy, minimally thickened competent valve leaflets at the distal end of the vein graft, a blind-ended popliteal artery, and a single patent residual arteriovenous fistula. At reoperation, patch angioplasty of the stenotic areas was performed (graft 9). In graft 28, angioscopy allowed accurate and rapid detection of a residual arteriovenous fistula.

Photographs that were taken from the videotape of selected angioscopic findings described above are shown in Fig 2.

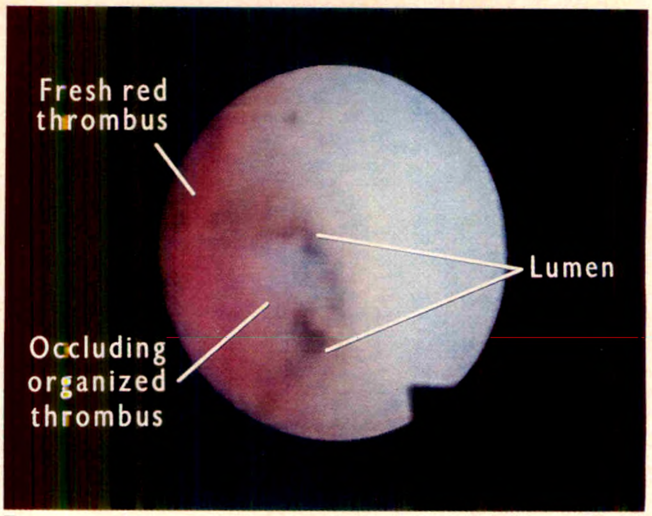
A summary of all the endovascular findings associated with graft failure is listed in Table 2.

COMMENT

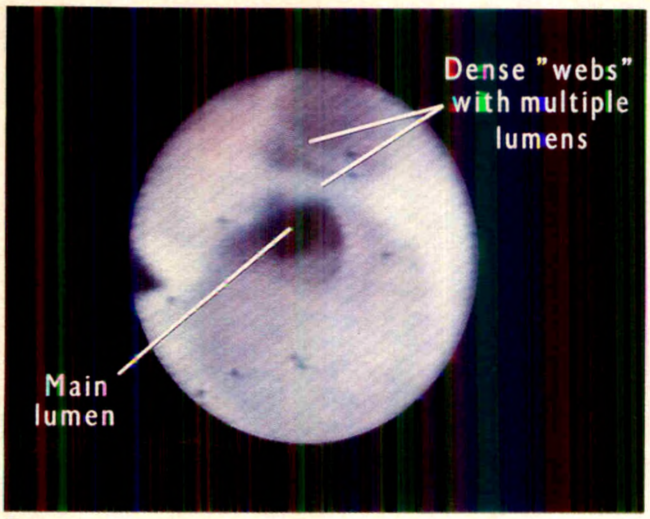
Our study shows that endovascular findings detected by angioscopy during the revascularization procedure, both of a


Large occluding atheromatous plaque
Blood clot (occluding ant. tibial)
Lumen (tibio-peroneal trunk)

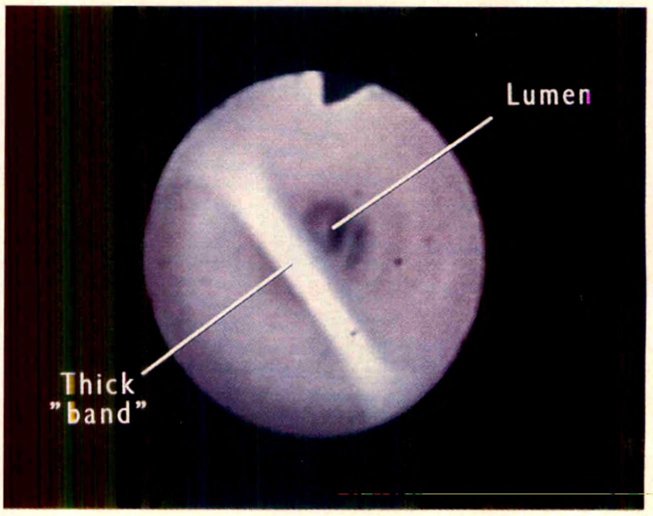
A


Fresh red thrombus
Lumen
Occluding organized thrombus

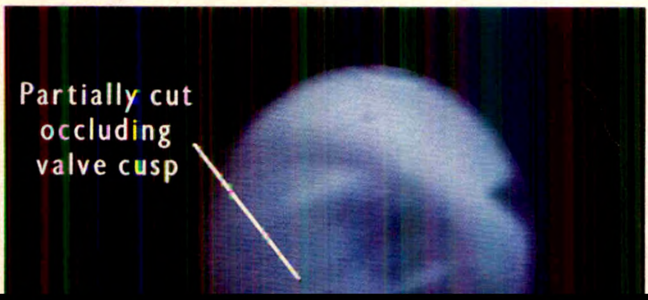
B

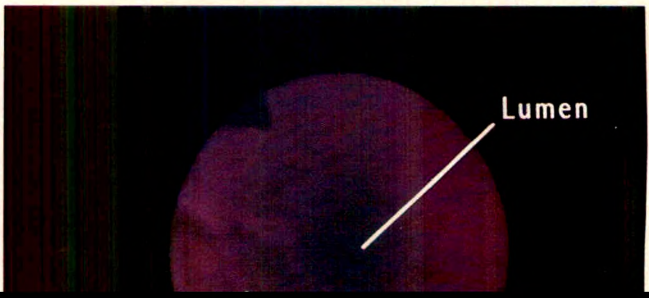

Dense "webs" with multiple lumens
Main lumen

E


Lumen
Thick "band"

F


Partially cut occluding valve cusp


Lumen

[redacted]

cross the lumen. The latter are especially noted around the valve leaflets.

Histologic examination of veins with webs show these to be recanalized organized thrombus within the lumen of the vein (Fig 1). External inspection of the vein does not usually identify the region of recanalization within the vein. We have shown that webs can cause graft failure (Table 1, graft 8), and we now recommend excision of that segment of the vein graft shown on angioscopy to have marked webs. The significance of the single bands or multiple strands is still uncertain other than to signify a vein of perhaps an inferior quality that

Table 2.—Angioscopic Findings Correlating With Graft Failure*

	Angioscopic Findings
Vein graft	Competent valve leaflets (unlysed/partially lysed), unligated tributaries (AV fistula), vein recanalization (webs/strands), thrombus (organized, platelet, fresh), mural sclerosis, intimal hyperplasia, sclerotic shortened valve leaflets, valvulotome-induced "injury," residual thrombus after thrombolysis, atherosclerotic degeneration

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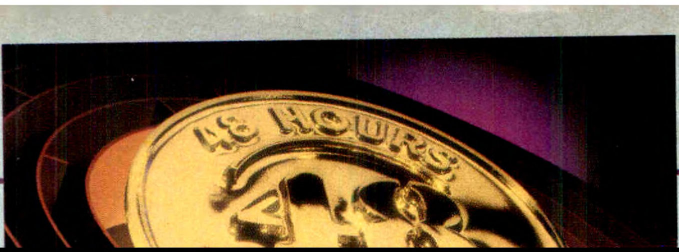

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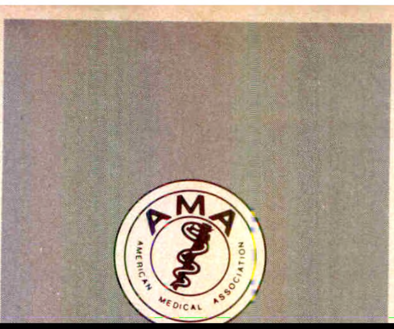

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AMA PATIENT

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Survey of Residents' Attitudes Toward Reform of Work Hours

Steven T. Ruby, MD; Lisa Allen, PhD; L. Peter Fielding, MD; Peter J. Deckers, MD

• **Traditional work schedules of surgical residents have been cited as a factor that negatively influences residency education and the quality of patient care. As an adjunct to the formulation of recommendations for the development of the environment for general surgery training, the New England Association of Program Directors in Surgery set out to sample the attitudes of surgical residents in New England relative to their perceived need to reform work hours. Seventy-two percent of the residents**

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RESULTS

Demographic Data

The 24 general surgery residency programs in the New England region were sent the questionnaires. Of the total 625 residents in these programs, 523 (84%) completed the questionnaire.

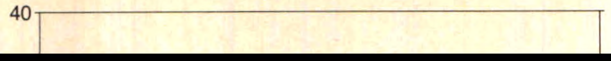

Table 2.—Influence on Attitudes of Perceived Need for Rest*

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COMMENT

The modern format of surgical training programs can be traced to the precepts of William Halsted and is based on the concept of progressive increase of individual clinical responsibility with appropriate levels of supervision. Long working hours have been an integral part of this philosophy and have become viewed by many as a necessary component of successful surgical training. Following the death of an 18-year-old woman in a New York, NY, hospital in 1984, long working hours were proposed to exert a negative influence on resident education and quality clinical care,[1] although it eventually became clear that fatigue had not been a factor in this case. A specific link between chronically fatigued house officers and decreased quality of care has never been firmly established. Sleep deprivation and chronic fatigue have been studied in detail in nonmedical professionals such as airline pilots and air traffic controllers.[2,3] We believe that a simplistic transfer of recommendations from such studies to the design and conduct of surgical training may be inappropriate.

The American College of Surgeons has rejected the concept that long working hours per se have a negative influence on clinical care and has specified that continuity of care is the

[redacted]

practice have been linked to sleep deprivation in several studies.[5,7,8] Schwartz and his colleagues[11] helped to put this subject into perspective by finding that medical and dental residents showed levels of stress only slightly above an adult comparison group using a symptom inventory, and that lack of sleep was only one of several factors identified that increased stress.

The results of our questionnaire indicate that the majority of residents in general surgery programs in New England perceive a need for reform of work schedules. Surgical educators have perhaps underestimated this sentiment in the past. As expected, an average resident works long hours and is on call slightly more than every third night. Most residents thought that long work hours impaired their educational experience and at times compromised clinical care. Residents in general were not in favor, for this reason at least, of lengthening the general surgery programs to 6 years. Physician assistants were embraced as positive solutions to potential coverage issues raised by regulating resident work schedules. Our analysis highlights the correlation between the perceived number of hours of sleep needed by a resident and the desire for work schedule reform. Stated simply, residents needing reasons for the degree of unrest in our training programs revealed by recent public debate and to evaluate the concerns of local and national politicians carefully. While it remains our responsibility to be responsive to these issues and to consider the personal needs of our residents, we must continue to maintain an established standard of excellence in education and clinical care and not to react to isolated, sensational exceptions without meaningful, compelling, quantitative data.

Joanne D'Aprile provided secretarial assistance during preparation of the manuscript.

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Discussion

Claude H. Organ, Jr, MD, Oakland, Calif: This is an important study that Dr Ruby and his associates have brought to us. Despite ongoing discussions, there are few data available today to make the decisions politicians have been loathe to make in this area. Libby Zion died at the New York Hospital in March 1984. This death created considerable discussion. The circumstances surrounding this death were really mislabeled. In December 1986, a New York grand jury issued its first report about this death. In October 1987, the Emergency Medical Services Committee of New York made specific recommendations, and in June 1988, the New York Resolution, Review and Planning Committee adopted the recommendations of the Emergency Medical Services Committee.

Dr Ruby's discussion and his collected data have reinforced my long-standing belief that the program director does not need to be a surgeon. He really needs to be a psychiatrist, spiritual advisor, manager, accountant, cheerleader, social worker, marriage counselor, and an arbiter. If he knows anything about surgery, that's a luxury as part of his job description, even though an increasing number like to stay out of the operating room.

Just a little demographic data: While the population of this country has increased 20% from 1970 to 1988, the total number of residents has increased by 119% while the surgical residents in the United States have increased by only 25% compared with 39% in the primary care specialties (*Socio-economic Fact Book for Surgery 1989*. Chicago, Ill: American College of Surgeons; 1989:9).

A recent California study showed that radiology residents had the highest percentage of moonlighting, averaging 13 h/wk; psychiatry, 12 hours; emergency medicine, 11.8 hours; dermatology, 9 hours; internal medicine, 8 hours; surgery, 7 hours; and pathology, no hours.

In the University of California study, they estimated that in terms of cost- effectiveness, to replace residents for a 72-hour work week with additional residents would cost $54 million; a nurse practitioner replacement would cost $154; and replacement with other physicians, $259. If they limited their work week to 80 h/wk, the cost for additional residents would be $39 million, $113 million for nurse practitioners, and $190 million for physicians. For a 90-hour work week, it would cost $26 million in additional salaries for residents, $75 million for nurses, and $125 million for physicians. These figures temper the impulsive actions of legislators.

There are alternate solutions being proposed. One is to limit working hours. Others are to develop alternative ways of covering night call, to assign patients to nonteaching services, to reassign resident duties to other health care professions in the hospital, to reduce the paperwork load with automated computerized records, to provide increased time off (they currently get a month off in most institutions), to provide personnel support services for residents (a legitimate area of concern), and to limit moonlighting. Those of you who watch the proceedings of the Resident Review Committee realize that there are specific (not spelled out as moonlighting) guidelines regarding their off-duty activities.

Objections to these problems being resolved in the public arena have been previously stated: There is a gray zone between the amount of time at work vs the amount of time invested in education. This would be the only group of graduate students whose hours would be regulated. Fatigue (and this was quite true in the Libby Zion case) is often confused with incompetence. There is concern that this practice will lead to less competent physicians or surgeons. We have never documented that patients have suffered from the phenomena of fatigue and sleep. We must object to and resist this widening control of education and the politicalization of our graduate system. The fact is that you cannot simply legislate good patient care, and you cannot legislate against every conceivable complication or wayward trend that goes on in society.

The whole matter of sleep is difficult to assess. I do not have a lot of objections to the comparison with airline crews and in the sleep requirements between flights. The all-American concept that you must have 8 hours of sleep a day has long since gone by the board. I am not even sure it is necessary. Some of our 40-year-old junior staff would have been sleeping for 12 years (it is one third of a day, so that would be 12 years) of their 40 years with this concept. The important thing about Rip Van Winkle was not that he slept for 40 years, but that he slept through a revolution.

Finally, let me remind you that in the October issue of the Archives (1989;124:1121-1122), there is a commentary by Robert Condon, MD, in which he states, "We need to move quickly before we are imposed on or imprisoned with the stifling embrace of additional naive and harmful government regulations. Time is running out." The easiest way for us to have politicians continue to intrude into this area is to sit down and do nothing. This report by Ruby and his associates is important, and should be thoughtfully considered.

L. Peter Fielding, MD, Waterbury, Conn: As Dr Ruby mentioned, this survey was conducted under the auspices of the New England Association of Program Directors in Surgery. As the current chairman of that fledgling group, I would like to thank all the program directors for participating and all the residents for their interests; 83% response rate is a very good return.

Perhaps two points need to be emphasized concerning the background reasons for conducting the survey. First, we recognized that there was much discussion about resident hours, their circumstances of employment and professional activity, but without significant input from the residents themselves. We thought it was time for a survey in which residents had an opportunity to participate.

The second reason has already been mentioned. In Connecticut and in Massachusetts, program directors have come under particular pressure by legislators questioning the motives of program directors in the conduct of their programs. It was thought that a good faith effort should be made to influence and convince the legislative people that we were, in fact, acting responsibly. This survey was one response to that perception.

In this presentation, we have not made reference to an "80-hour week" because we agree with other national professional organizations that 80 hours as a legislative number would be entirely inappropriate, particularly in the setting of surgical education.

Charles P. Shoemaker, Jr, MD, Newport, RI: Although warned about extrapolating, I cannot resist talking about the need for sleep in the context of a community hospital. Forgetting surgeons for a moment, when we return home Monday morning we may see an anesthesiologist, a member of the nursing staff, or an obstetrician

Residents' Hours—Ruby et al 767

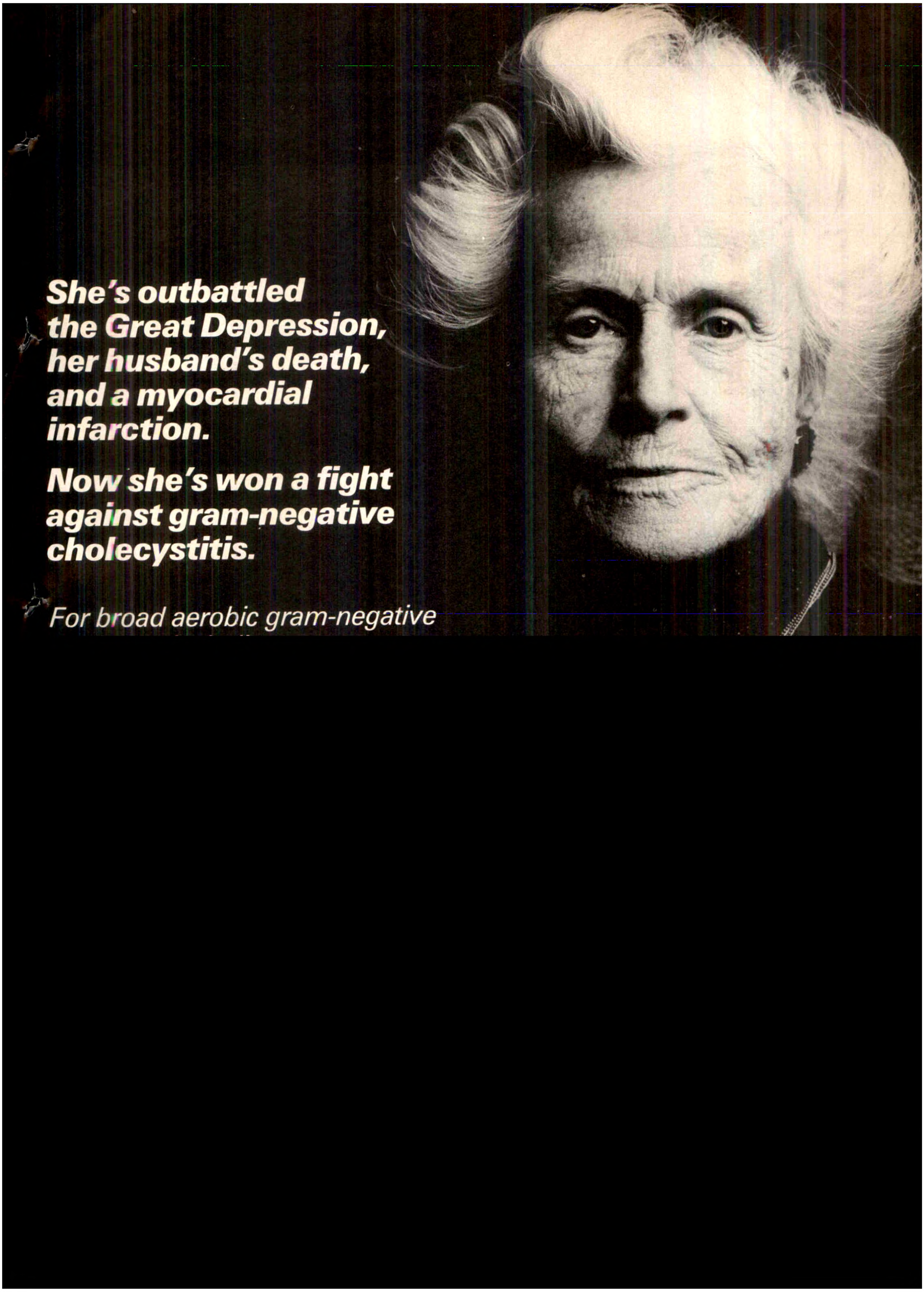
who has been up all weekend; they seem to brag about how many cases they did and yet they are there Monday morning. We talk about quality care and the residents. I cannot say they have documented the need for sleep, but they have indicated that the quality of care is impaired by the lack of sleep. I think it is a need that we all have to look at. I see community hospitals making manpower plans for their hospitals based on the number of physicians for the size of the community, but I do not think we are looking at how many hours they are working and I think we have to.

DR RUBY: There are basically two points that I would like to make.

[redacted]

coming out of our training programs today is excellent. It is as good as it ever was, and maybe it is getting better. I do think that the quality of the patient care rendered by our residents is equally as good.

The second closing point I would like to make has to do with what was talked about earlier in this meeting. We must take the ball here and run. If we don't, others will do it for us and I think we are going to find a system that will be very uncomfortable for us to fit into. So, I take this as a challenge and hope that over the next several years we can look at this more critically and come up with a situation that will be very tolerable and very acceptable to the American public and to surgeons in general.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Carcinogenesis, Mutagenesis, Impairment of Fertility—Carcinogenicity studies

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PATIENTS AND METHODS

A total of 928 women with UICC-AJCC clinical stage I or II breast cancer according to the classification of the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer (UICC) were treated at the JCRT between July 1968 and December 1982. To eliminate the confounding effects of possibly inadequate treatment, 31 patients who had less than excisional biopsy (ie, needle biopsy or incisional biopsy only) and 114 patients who received a total dose of less than 60 Gy to the region of the primary tumor were excluded from the analysis. The study population thus consisted of 783 patients. In contrast to our previous studies, patients who presented with simultaneous bilateral tumors were excluded from this study, and for patients with a metachronous opposite breast tumor, only the first tumor was considered in the analysis of breast recurrence. As of December 1988, median follow-up was 91 months for 587

extent of intraductal carcinoma within the infiltrating primary tumor and the adjacent grossly normal breast tissue, for tumors of infiltrating ductal histologic type.

Tumor measurement was obtained prospectively before definitive treatment in all patients and was performed by the attending surgeon and/or radiation therapist. In fact, measurement of the tumor represents the clinical staging (either physical examination or mammographic abnormality, whichever is larger). All patients entered into this prospective study had a breast cancer staging sheet, similar to the AJCC form currently in use, that was prospectively completed before definitive surgical management.

An EIC-positive tumor was defined as an infiltrating ductal carcinoma in which intraductal carcinoma was prominent within the tumor (often corresponding to 25% of the tumor area) and present in adjacent grossly normal breast tissue. In addition, tumors classified as predominantly intraductal carcinoma with one or more areas of mi-

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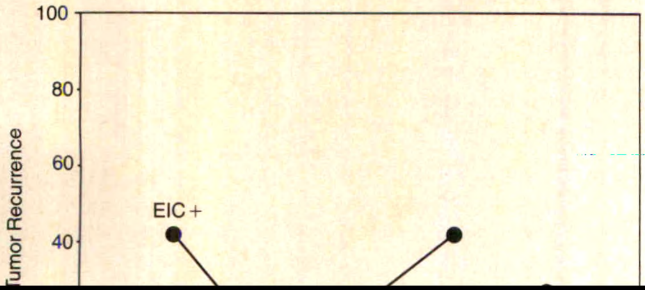
Table 1 shows the analysis of local recurrence among the subgroup of 584 assessable patients with infiltrating ductal carcinomas in whom the intraductal component could be evaluated. These are divided into the categories of EIC negative or EIC positive. Among the 418 patients with EIC-negative tumors, there were 31 local recurrences (7%). Therefore, among patients with EIC-negative tumors, increasing tumor size was not associated with increased local recurrence. Once again, the highest local recurrence rate was in the 0- to 1-cm tumor size (8 [11%] of 70). In the patients who had EIC-positive tumors, there was an overall 27% (44/166) local recurrence rate. Again, there was no trend toward increasing rate of local recurrence with increasing tumor size within this category. As seen with EIC-negative tumors, one of the highest local recurrence rates was in the tumor size category of 0 to 1 cm (14 [42%] of 33). However, as seen in Table 1, for every tumor size, the presence of extensive intraductal carcinoma predicted for a statistically higher local recurrence rate when compared with EIC-negative tumors. This is also seen in Fig 2, which graphically shows the local recurrence rate for each tumor size for the EIC-negative tumors as well as the EIC-positive tumors.



COMMENT

The results of this study of 783 patients followed up for a median time of 91 months demonstrate that local recurrence in the breast in patients treated with conservative surgery and radiation therapy is not related to the size of the primary

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T2 and N0 or N1 patients with breast cancer who were treated with radical external beam radiation and interstitial iodine 92 iridium implants. These authors found that size was an important factor, as there was a clear difference in local control between T1 and T2 clinical tumor stages. However, within the T2 subgroup, size became less important, with no significant difference in recurrence observed between those with tumors smaller than 3 cm and those with tumors larger than 3 cm. Additionally, only 22% of the patients with T2 clinical stage tumors had a tumorectomy performed, thereby contributing to an increased tumor burden in the larger tumor sizes prior to the onset of radiation therapy. In contrast, all of our patients had gross excision of the palpable tumor or mammographic abnormality.

Table 2 documents 10 nonrandomized trials and 4 randomized trials in the literature[17-29] documenting the relationship to tumor size and local recurrence rate. As can be seen in this

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had a 74% likelihood of having residual tumor (predominantly intraductal carcinoma) found beyond the edge of the primary tumor. In contrast, reference breast cancers that were EIC negative had a 42% chance of having such residual tumor. Furthermore, 44% of patients with EIC-positive tumors had prominent residual intraductal carcinoma compared with only 3% of patients with EIC-negative tumors. These findings are consistent with the hypothesis that EIC-positive tumors are associated with a higher rate of subsequent recurrence in the breast following limited excision and radiation therapy, because they have a greater residual tumor burden in the breast than do EIC-negative tumors.[33] The results of our study are consistent with this hypothesis.

We have previously described predictors for local recurrence among our patients with breast cancer treated with conservative surgery and radiation therapy.[11,14] In these reports, we showed that an EIC-positive tumor was the princicosmetic results, tumor size per se is not a contraindication for conservative surgery and radiation therapy.

In conclusion, tumor size does not predict local recurrence of breast cancer following conservative surgery and radiation therapy. This is true whether the tumor is ERP positive, ERP negative, EIC negative, or even EIC positive. However, EIC-positive tumors are associated with a significant risk of local recurrence regardless of tumor size, indicating that these patients are not adequately treated with simple excision and radiation therapy. If patients with EIC-positive tumors are to be considered for breast-conserving treatment, wider resection and establishment of tumor-free margins are recommended.

We thank Regina Muehe for her assistance in compiling the estrogen receptor data, and the Department of Pathology staff, New England Deaconess Hospital and the Brigham and Women's Hospital, Boston, Mass, for their continued cooperation. We also thank Elaine Collins and Pauline Hurley for preparation of the manuscript, and Barbara Silver for data analysis and review of the manuscript.

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(Continued from previous page.)

California Kaiser; size of tumor did not predict local recurrence, but a small size of the excised specimen correlated strongly with local recurrence. Kantorowitz et al (*Radiother Oncol.* 1989;15: 141) reported an uncontrolled series of 146 patients from Rochester, NY; size of tumor did not correlate with local recurrence, but local recurrence was much less common in patients treated with the widest surgical excisions (quadrantectomy). In the Milan trial

form the range of maximum comfort for the surgeon and are most likely to result in adequate margins, as the authors' data suggest.

It is important not to misinterpret what this study found. The size of the primary tumor is critically important to the outcome of patients with cancer of the breast. In just considering reports dealing with the larger series published in the past year, detection of cancers at small sizes by mammographic screening has been confirmed to reduce the incidence of subsequent death from

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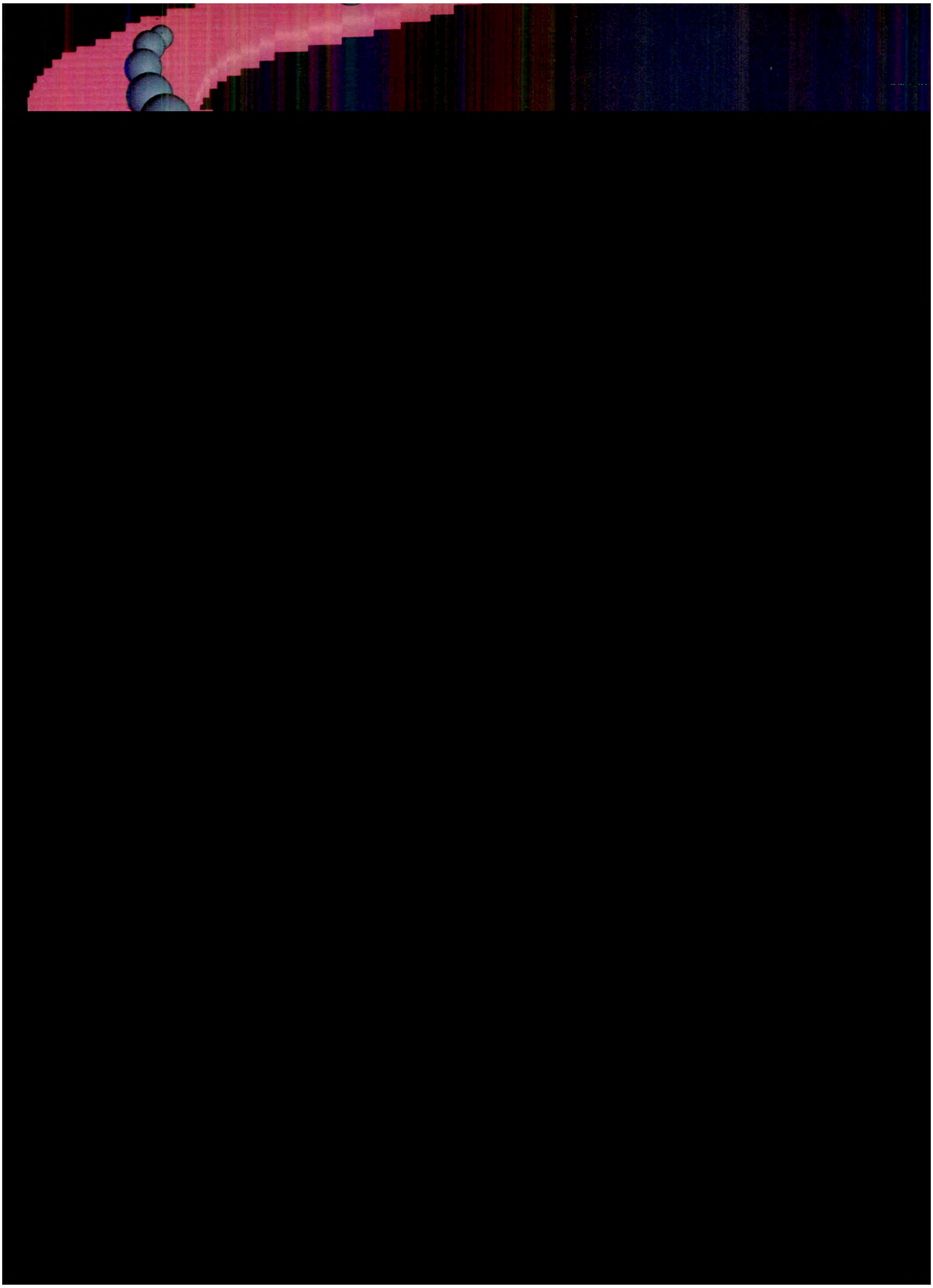

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BRIEF SUMMARY

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Table 1.—Pretransplant Patient Characteristics

Characteristic	Control Group	OKT3 Group
N	41	38
Age, y	45.1 ± 12.4	46.5 ± 13.4
No. (%) male	21 (51)	22 (58)

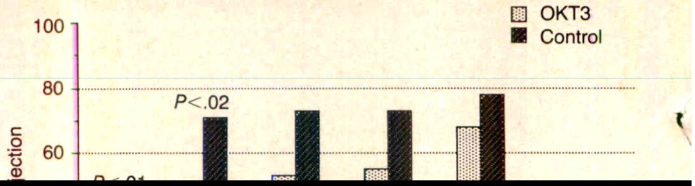

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Table 2.—Treatment of Hepatic Allograft Rejection

	No. (%)	
	Control Group (N=41)	OKT3 Group (N=38)
Rejection	32 (78)	26 (68)
Steroid responsive	10 (31)	21 (81)

types of allografts. Several preliminary trials have suggested that OKT3 or other antilymphocyte sera might also be effective when administered as part of the prophylactic immunosuppressive regimen rather than only after rejection has been diagnosed.[10,11] Recently, Millis et al[12] reported in a randomized study of 52 liver allograft recipients that prophylactic OKT3 resulted in a lower incidence of early rejection and a decrease in renal dysfunction. Early (6-month) patient survival was

[redacted]

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Fenestration Revisited

A Safe and Effective Procedure for Descending Aortic Dissection

John A. Elefteriades, MD; Graeme L. Hammond, MD; Richard J. Gusberg, MD; Gary S. Kopf, MD; John C. Baldwin, MD

• Although it was initially performed in 1935, aortic fenestration has been infrequently employed and reported in recent years. We have continued to use fenestration for descending aortic dissection with complicating organ ischemia (lower-extremity ischemia, renal ischemia, and paraplegia). Our technique involves complete transection of the infrarenal abdominal aorta, removal of a generous intimal flap proximally, and reconstitution of layers distally. We report our experience with 12 patients, all of whom survived the operative procedure. Nine patients were discharged from the hospital, and with a mean follow-up of 6.8 years, 7 are still alive. Fenestration immediately restored organ perfusion in all but 1 of the patients, and no patient died of late rupture. We recommend fenestration for descending aortic dissection in patients presenting with organ ischemia. Fenestration is not recommended for acute dissection with rupture or for chronic enlarging dissection.

(*Arch Surg.* 1990;125:786-790)

Aortic fenestration, also known as "the reentry procedure," was used in the early years of surgical treatment for acute aortic dissection but is not widely used today. We have performed fenestration as our primary procedure for descending dissection with limb compromise. We report herein our experience using this procedure in the treatment of 12 patients during the last 15 years.

Our goal in this study was to evaluate the safety and efficacy of the fenestration procedure. In particular, we sought to answer the following questions:

1. What is the mortality and morbidity of the fenestration procedure?
2. Does fenestration effectively restore perfusion below the level of the procedure (ie, to the lower limbs) and above the level of the procedure (ie, to kidneys, intestines, and spinal cord)?
3. How is fenestration best performed technically?
4. What is the proper timing for fenestration?

[redacted]

vors of aortic dissection. DeBakey et al described six patients who were treated surgically for aortic dissection, two with fenestration. One of the patients treated with fenestration was a long-term survivor, representing the first recorded survivor of dissection treated with fenestration. In 1956, Swann and Bradsher[5] reported a case of a survivor of a fenestration procedure that had to be performed immediately at the time of dissection.

Few fenestration procedures were reported in subsequent years.[6-12] Beckwith et al in 1959,[6] Rob and Kenyon in 1960,[7] Thomas in 1961,[8] Amer et al in 1962,[9] Hume and Porter in 1963,[10] and Stern in 1964[12] reported cases of surgical treatment of aortic dissection that included fenestration. All of these authors found this technique to be useful and successful in selected cases. In 1976, Hunter et al[11] recommended fenestration combined with placement of an aortic bifurcation graft for the treatment of patients with aneurysmal dilatation of the abdominal aorta associated with aortic dissection.

Aside from occasional mention in reviews of surgical treatment of aortic dissection or in textbooks, fenestration has received little attention, especially in recent years. The recent sentiment has been that fenestration is of historical interest but has been supplanted by more modern techniques. The purpose of this report is to present our experience with this procedure in recent years, demonstrating its importance in the current armamentarium of techniques for the surgical treatment of aortic dissection.

PATIENTS AND METHODS

The records of all patients admitted to Yale–New Haven (Conn) Hospital with aortic dissection between 1974 and 1988 were reviewed. A total of 45 patients underwent treatment for descending aortic dissection during this period.

During the period 1974 through 1988, our policy was to perform fenestration in all patients with acute descending aortic dissection

[redacted]

Clinical Experience With Fenestration Procedures							
Patient/ Age, y/ Sex	**Type of Dissection**	**Indication(s) for Surgery**	**Operation**	**Hospital Survival**	**Reperfusion**	**Late Survival Cause of Death**	**Comment**
1/58/M	Ascending	Leg ischemia	Standard	Yes	+	Died (36 mo)	Presented with ascending dissection; treated as descending dissection as had

[redacted]

tion, we recommend this procedure for acute aortic dissection presenting with branch vessel occlusion. This presentation is

[redacted]

tration at this point in our experience for acute dissection presenting with rupture or impending rupture; we continue

(Table 2). In group 1, primary closure was performed in 11 HDs, with 7 postoperative infections (64%). In group 2, primary closure was performed in five HDs, with three postoperative infections (60%). In group 3, primary closure was performed in four HDs, with two postoperative infections (50%). Overall, 12 postoperative infections (60%) occurred in 20 HDs performed with primary closure.

Eighteen HDs were judged to have a severe preoperative extremity infection. In an effort to prevent closing a heavily contaminated wound, all of these wounds had fascial closure, and the skin and subcutaneous tissue were left open to granulate. Postoperatively, 12 (67%) of 18 HDs with preoperative infection developed an overt superficial wound infection.

Hemorrhagic shock occurred in 4 (11%) of 38 HDs, contributing to death in 3 patients. All of these deaths occurred in group 3 patients, who had the largest mean blood loss (2636 mL [range, 400 to 7000 mL]). The next largest mean blood loss was seen in group 2 patients, at 1240 mL (range, 300 to 3000 mL), followed by group 1 patients, with a mean blood loss of 879 mL (range, 100 to 5000 mL). Perioperative coagulopathy developed in four HDs, contributing to three deaths. All of these deaths were in group 3 patients.

Four patients undergoing four HDs had preoperative chronic renal insufficiency. Eight patients undergoing nine HDs had postoperative renal insufficiency, contributing to death in six patients. Postoperative renal insufficiency was associated with preoperative renal insufficiency, shock, myoglobinuria, and aminoglycoside nephrotoxic effects.

Cardiac dysfunction developed postoperatively after 10 HDs, including those in seven patients with congestive heart failure and three patients with new rhythm disturbances. Five patients with congestive heart failure and two patients with rhythm disturbances died. Sixty percent of all patients with cardiac dysfunction were in group 1.

Postoperative pulmonary dysfunction developed in 9 (24%) of 38 HDs. Six of these patients were in group 1. Pneumonia developed in 3 patients. Pulmonary insufficiency requiring tracheal intubation and adult respiratory distress syndrome developed in 6 patients, contributing to 5 deaths.

Twenty HDs were performed on extremities with previous amputations (19 above the knee and 1 below the knee). Thirteen of these previous amputations had been performed dur-

Table 1.—Indications for Hip Disarticulation (HD) and Mean Age of Patients

Group	Indications for HD	No. of Patients	No. of HDs	Mean Age, y
1	Ischemia secondary to atherosclerosis	15	17	63.1
2	Femoral osteomyelitis	9	10	41.4
3	Ischemia secondary to trauma	10	11	39.1

Table 2.—Wound Infection Analyzed According to Type of Wound Closure*

Group	Wound	No. of HDs	No. of Patients	No. of Clinical Preoperative Infections	No. of Clinical Postoperative Infections (% of HDs)
1	**Total**	**17**	**15**	**11**	**10** (59)
	Primary closure	11	10	5	7 (64)
	Open	6	5	6	3 (50)
2	**Total**	**10**	**9**	**10**	**8** (80)
	Primary closure	5	4	5	3 (60)
	Open	5	5	5	5 (100)
3	**Total**	**11**	**10**	**4**	**6** (55)
	Primary closure	4	4	1	2 (50)
	Open	7	6	3	4 (57)
Total	. . .	**38**	**34**	**25**	**24** (63)

*HDs indicates hip disarticulations.

Table 3.—Hip Disarticulations (HDs) Analyzed According to Presence or Absence of Preoperative Extremity Infection and Its Influence on Mortality

Preoperative	No. of	No. of	No. of Clinical Postoperative	No. of Deaths (% of

[redacted]

Continuous, 10-Year Wound Infection Surveillance

[redacted]

ter *and* if skin edges were concomitantly inflamed, these wounds were judged to be infected. Wounds that drained sterile serous fluid or displayed cellulitis, or skin suture tract abscesses not in contact with the surgical incisional space, were carefully observed for suppuration, but none of these three settings automatically triggered a diagnosis of wound infection. Purulent collections that were anatomically remote from and not naturally draining through the subcutaneous strata of surgical incisions were defined as abscesses and have been reported separately.[26]

Risk Classification of Wounds

Operating room nurses classified operative wounds according to infection risk, and the nurse epidemiologist was responsible for teaching risk classification methods to these colleagues. Three wound classes, adapted from those of the American College of Surgeons

gist to a combined morbidity conference of general, vascular, cardiothoracic, head/neck, transplant, and proctologic surgeons. Allowing for 30-day follow-up expiration, this schedule guaranteed that every wound infection was formally presented within 30 to 60 days of the corresponding operation date. The same data were provided to urologists, orthopedic surgeons, ophthalmologists, neurosurgeons, and the otolaryngologists for separate monthly reviews. In this fashion, all surgeons were regularly made aware of all wound infections on all services. Monthly printed summaries were forwarded in a standard format to the hospital infection control committee, chief of nursing, anesthesia department, and operating room nurses for monthly review.

Complete printed reports were generated at 6- and 12-month intervals as well, with copies provided to every surgeon on the staff. Wound infection data were not stratified to generate surgeon-specific

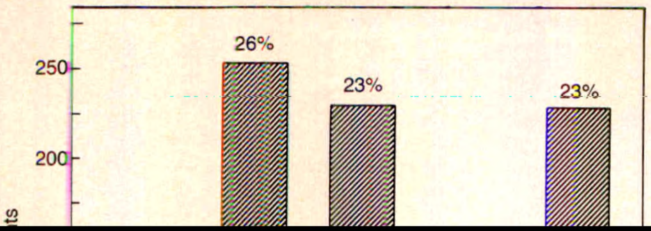


Table 1.—Overall Wound Infection Rates

Year	Total No. of Operations	Total No. of Infections	Rate, %*
1977	4476	188	4.2
1978	4335	120	2.8
1979	3969	97	2.4

[redacted]

Table 3.—Wound Infection Rates by Risk Class*

Year	Class I			Class II			Class III		
	Operations	Infections	Rate	Operations	Infections	Rate	Operations	Infections	Rate
1977	2699	61	2.3	1363	74	5.4	414	53	12.8
1978	2686	40	1.5†	1217	42	3.5†	432	38	8.8
1979	2502	41	1.6	1089	24	2.2†	378	32	8.5†
1980	2324	38	1.6	1065	25	2.4†	419	38	9.0
1981	2241	18	0.8†	1021	13	1.3†	362	37	10.2
1982	2387	23	1.0†	1067	17	1.6†	444	29	6.5†
1983	2515	24	1.0†	1009	27	2.7†	390	20	5.2†
1984	2808	36	1.3†	1040	29	2.8†	412	31	7.5†
1985	2936	50	1.7	966	30	3.1†	430	35	8.0†
1986	2821	42	1.5†	938	23	2.5†	540	42	7.8†
Total	**25 919**	**373**	1.4	**10 775**	**304**	2.8	**4221**	**355**	8.4

*Data are given as the number of operations and infections; the wound infection rate is given as a percentage.

†$P<.05$ for comparison with the 1977 rate.

Wound Infection Reductions by Specialty

The impact of our program was measured by comparing rates from pooled 9-year infection data to index year infection rates (Table 5). The underlying assumption here, that maximal reduction in wound infection rates occurred during the first year of surveillance, is supported by findings of other investigators.[3,4,6,8,17,24] Statistically significant infection rate reductions in all risk classes stimulated a search for the responsible specialty services. Notably, their identities were not predictable from overall infection rates (Table 6), or the individual specialty shares of the total infection problem (Fig 4). Significant reductions in wound infection occurred on three services (Table 7). The other eight operating services, together accounting for 54% of the total 10-year surgical caseload, individually demonstrated no significant changes in any risk class rates. Mathematically, the potential for improving wound infection rates existed only for surgical specialties that had correct combinations of case volume, risk mix, and relatively high index year rates in one or more risk classes. Our work shows that global surveillance (ie, investigating all wound infections) allows identification of both those specialties that should consider changing prevention efforts, as well as specialties that should continue their infection control measures unchanged.

Interventions

Our overall (Fig 5) and risk-stratified (Fig 6) wound infection rate improvements seemed to be related initially to only sensitization and encouragement of surgeons, because we identified no educational or correctional events during the first year. During 9 subsequent years of surveillance, however, periodic clinical interventions were made to attack problems identified by the program. Such interventions, together with the continuous influence of the more subtle effects of surveillance, have probably acted to maintain our wound infection rates at acceptable levels to date. For example, in 1977, it was a policy to shave body hair preoperatively from all surgical sites. When a class I vascular surgery wound infection rate of 6% in 1978 was investigated by the nurse epidemiologist, it was discovered that many patients were being routinely shaved 24 hours before operation. Subsequently, a department-wide policy discontinued skin shaving in favor of electric clipper use. Data that substantiated the wisdom of this policy[32] were generated in the continuous follow-up that was made possible by the surveillance program. Several instances of flawed preoperative skin preparation[33] were identified and corrected, and optimum class III wound management, an old surgical issue,[34-36] was confronted. Analysis of the 1977 infection data showed that half of class III wound infections had followed general surgical procedures in which skin wounds had been primarily closed. Vigorous educational efforts were made, and in the subsequent 9 years, primary skin closure was identified in only 14% of class III infections. This simple technical change has probably played a significant role in reducing our class III infection rate.

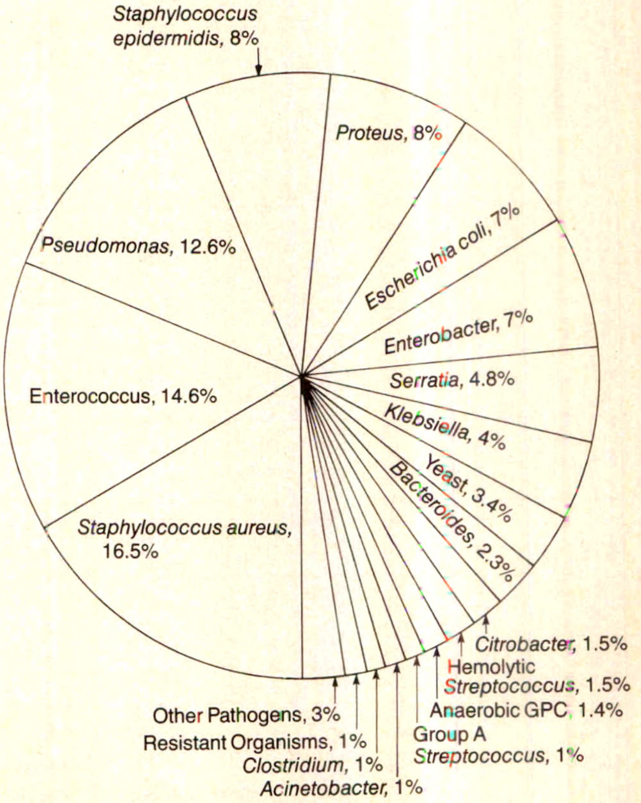


Fig 3.—Surgical wound infection pathogens isolated from 1977 through 1986. GPC indicates gram-positive cocci.

Prophylactic Antibiotics

Parenteral antibiotics, used appropriately, undeniably reduce wound infection rates. The pertinent biologic issues

Table 4.—Organisms Cultured From 1032 Infected Wounds During 10-Year Surveillance Period

Pathogen	Isolates, No. %	Wound Class, No.		
		I	II	III
Staphylococcus aureus	240 (16.5)	140	51	49
Enterococcus	212 (14.6)	63	70	79
Pseudomonas	183 (12.6)	38	52	93
Staphylococcus epidermidis	118 (8.1)	59	26	33
Proteus species	114 (7.9)	38	37	39
Escherichia coli	105 (7.2)	20	46	39

have been exhaustively studied,[37] and prophylaxis is indicated for class II and III operations, as well as for certain class I operations. Three kinds of antibiotic prophylaxis errors were identified. A large majority (86% to 98%) of our infected patients had undergone operations for which antibiotic prophylaxis was definitely indicated (Table 8). There was either omission of, or failure to give in timely fashion, preoperative antibiotics to almost one third of patients with infections throughout 1978 and 1979. During the following 8 years, these errors decreased significantly. The value of a focused investigation by a nurse epidemiologist is illustrated by her discov-

[redacted]

ery that preoperative antibiotics were sometimes properly ordered by surgeons without charted proof of their injection (within 2 hours before or 1 hour after skin incision) by either ward nurses or anesthesia personnel. This error, although infrequent, provided a basis for stimulating better nurse charting and clarified a policy of having nurse anesthetists inject prophylactic antibiotics just after induction.

Antibiotic Prophylaxis and Infected Wound Cultures

The finding that prophylactic antibiotics had not "covered" wound infection pathogens in 32% to 64% of infected patients throughout 10 years (Table 8) does not necessarily represent flawed drug selection and must be carefully interpreted. In view of our decreasing wound infection rate trends in every risk class, such "antibiotic failure" more likely represents the predictable outcome of prophylaxis reaching its biologic limits. Interestingly, three organisms (enterococcus, *Pseudomonas*, and *S epidermidis*), resistant to our nearly universal prophylactic drug, cefazolin sodium, together accounted for a majority (53%) of the wound infections that followed seemingly adequate prophylactic drug use. Viewed from another perspective, Table 8 also shows that 36% to 68% of wound infection organisms were *sensitive* to administered agents, confirming that antibiotic prophylaxis is not foolproof and strongly implicating the added influences of covariables, such as host-defense deficits, surgical technique errors, or overwhelming intraoperative bacterial inocula. We believe that the rational response to wound infection isolate resistance data should be case-by-case analysis of pathogens and the associated operations to determine if apparent antibiotic failures cluster for specific services or procedures. We presently have no evidence to support a department-wide change to different, and perhaps more expensive, prophylactic antibiotic agents. Although the identification of antibiotic resistance is almost never required for treatment of the large majority of wound infections, this information can be important. For example, infections by dangerous organisms, such as the resistant strains of *S aureus*,[38] are identified immediately by a program such as ours, allowing special measures to be taken to prevent their hospital-wide spread. Another example of our program's utility is provided by the unexpected observation of unusual positive bile cultures from six cholecystectomies. Culture of gallbladder bile is essentially routine in our hospital, and the nurse epidemiologist has compared operative bile cultures with biliary procedure wound infection cultures since 1979. During 1984, the ominous finding of six bile cultures yielding *Pseudomonas aeruginosa* stimulated a special investigation. It was discovered that all six patients had undergone endoscopic retrograde cholangiopancreatography procedures preoperatively and that a particular gastroduodenoscope had been contaminated with the organism but improperly cleaned between patients. Rapid corrective action was possible because of our surveillance program and its reporting function.[39]

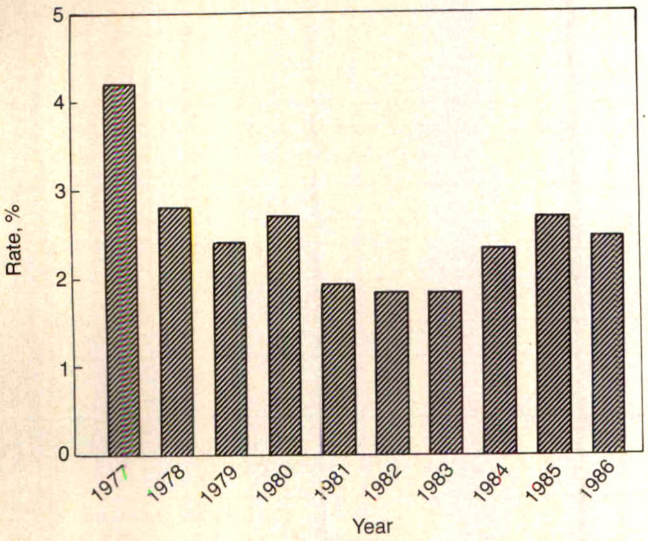
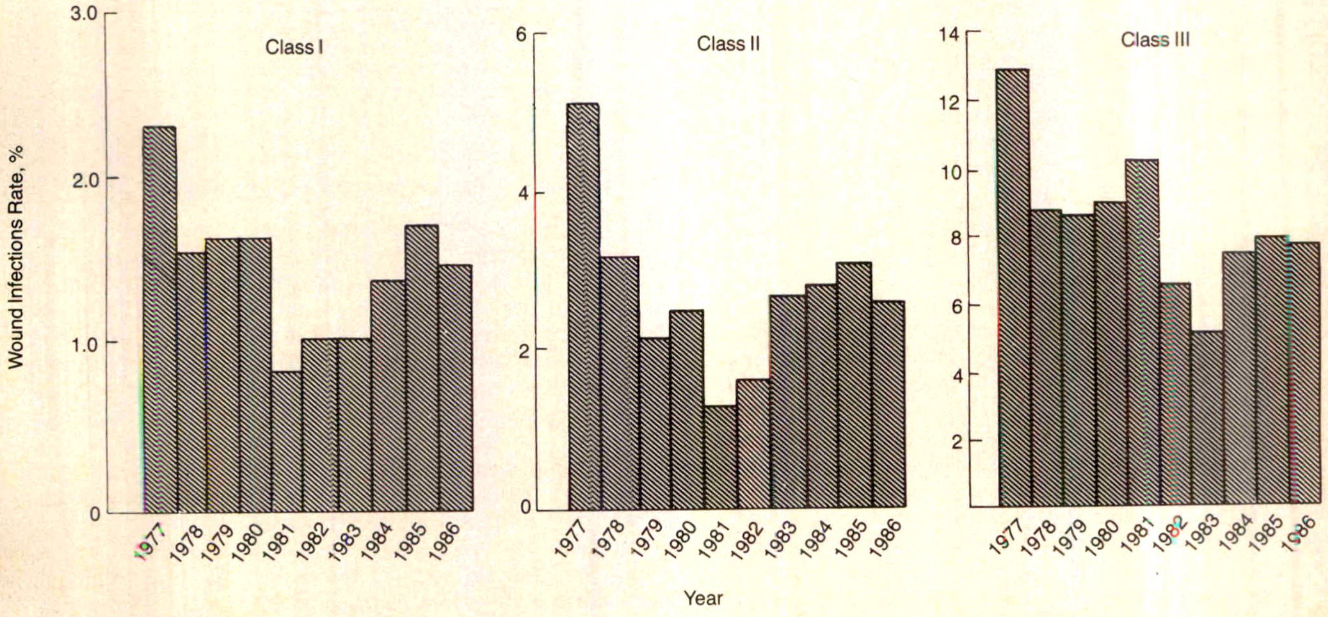


Fig 5.—Overall surgical wound infection rates from 1977 through 1986.

Estimated Cost Savings

A strong argument for minimizing surgical wound infections is that such complications, while seemingly infrequent

Fig 6.—Risk class infection rates from 1977 through 1986. Class I indicates clean; class II, clean contaminated; and class III, contaminated.



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within conventional risk classes. Comparison of procedure-specific wound infection rates is a further refinement. Our

Table 13.—Timing of Wound Infection Diagnosis Relative

[redacted]

Clinical Note

Mondor's Disease Secondary to Intravenous Drug Abuse

Richard A. Cooper, MD

• This article reports Mondor's disease resulting from intravenous drug abuse. This cause of Mondor's disease has never been described. Increased awareness should lead to increased

[redacted]

breasts as an injection site. She was diagnosed as having thrombophlebitis of her breasts, both internal jugular veins, and superior vena cava. Placement of internal jugular lines probably contributed

She was successfully treated with anticoagulants. Eight months later she was brought to the hospital dead on arrival. No autopsy was performed.

COMMENT

Mondor's disease was popularized by French surgeon Henri Mondor in 1939[1] as superficial thrombophlebitis of the anterior thoracoabdominal wall. It has a 3:1 female-male ratio and classically presents as a painful, palpable, and sometimes visible subcutaneous cord. Spontaneous resolution usually occurs in 2 to 4 weeks, but Fischl et al[2] report recanalization taking as long as 4 months. Millar[3] suggests division of the cord when it is painful or crosses a joint and, thus, limits movement.

The etiology of Mondor's disease is unknown but, like any superficial phlebitis, it may be related to direct trauma, surgery, biopsy, infection, bandaging, or tight clothes. Camiel[4] suggests that pendulous breasts may be causative, and Burns[5] discusses its occurrence on the chest wall after mastectomy.

Though it is overwhelmingly a benign condition, several authors[6-8] report the association of Mondor's disease with breast cancer. Perhaps the phlebitis is due to extrinsic compression by either the primary cancer or by metastatic axillary nodes.

In this case, mammography was ordered because of suspicion of inflammatory carcinoma as well as the inability to perform adequate breast palpation. It is likely that the patient's multiple breast injections and the placement of internal jugular lines led to her superior vena cava thrombosis, which mimicked inflammatory carcinoma.

Another patient soon entered the hospital and presented with a breast abscess resulting from intravenous drug abuse. Breast injection was her preference over an arm site, as track marks are easily hidden. She was also a prostitute. She stated that she preferred to inject the inferior aspects of her breasts because this allowed her to continue to wear revealing clothing. Coincidentally, the inferior aspect of the breast is the most common site for idiopathic Mondor's disease. She stated that most of her associates are addicts and 50% use their breasts as a primary injection site.

Breast injection is, thus, reported as another cause of Mondor's disease. In this case, the Mondor's disease may have contributed to superior vena cava thrombosis. The edema resulting from the superficial thrombophlebitis and the superior vena cava obstruction created the clinical suspicion of inflammatory breast carcinoma. Increased awareness should lead to increased recognition, as intravenous drug abuse is so pervasive.

Gail Bendict, RT, provided her expertise in mammographic technology.

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Books

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HEMATOLOGIC—eosinophilia (6%), thrombocytosis (5.1%) and leukopenia (2.1%). Less frequently reported (less than 1%) were anemia, neutropenia, lymphopenia, thrombocytopenia and prolon-

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PAPERS READ BEFORE THE 97TH ANNUAL MEETING OF THE WESTERN SURGICAL ASSOCIATION, ST LOUIS, MO, NOVEMBER 14 TO NOVEMBER 15, 1989—PART I

Responsibilities of General Surgery: Training for the Future: Presidential Address 829
J. Bradley Aust, MD, PhD, San Antonio, Tex

Metatarsal Head Resection for Diabetic Foot Ulcers 832
Gareth David Griffiths, FRCS, Thomas Jeffery Wieman, MD, Louisville, Ky
- Metatarsal head resection is recommended to achieve healing of the chronic diabetic foot ulcer under the metatarsophalangeal joints.

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- Nonoperative management of blunt hepatic injuries is a useful alternative in hemodynamically stable patients supported by computed tomography.

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- Insulin and the epidermal growth factor act synergistically for a net gain in wound collagen content.

Hydroxyethyl Starch Macromolecules Reduce Myocardial Reperfusion Injury 930
Bashir A. Zikria, MD; Chivukula Subbarao, MD; Mehmet C. Oz, MD; Sulli J. Popilkis, DVM; Ranjit Sachdev, MD; Prem Chauhan, MD; Harold P. Freeman, MD; Thomas C. King, MD, New York, NY
- Hydroxyethyl starch Pz reduces myocardial reperfusion injury in the canine model.

CLINICAL NOTE

Metastatic Pheochromocytoma Associated With Multiple Endocrine Neoplasia Syndrome Type II 935
Aaron H. Chevinsky, MD; John P. Minton, MD, PhD; James M. Falko, MD, Columbus, Ohio
- Surgical debulking of a metastatic pheochromocytoma provided significant palliation.

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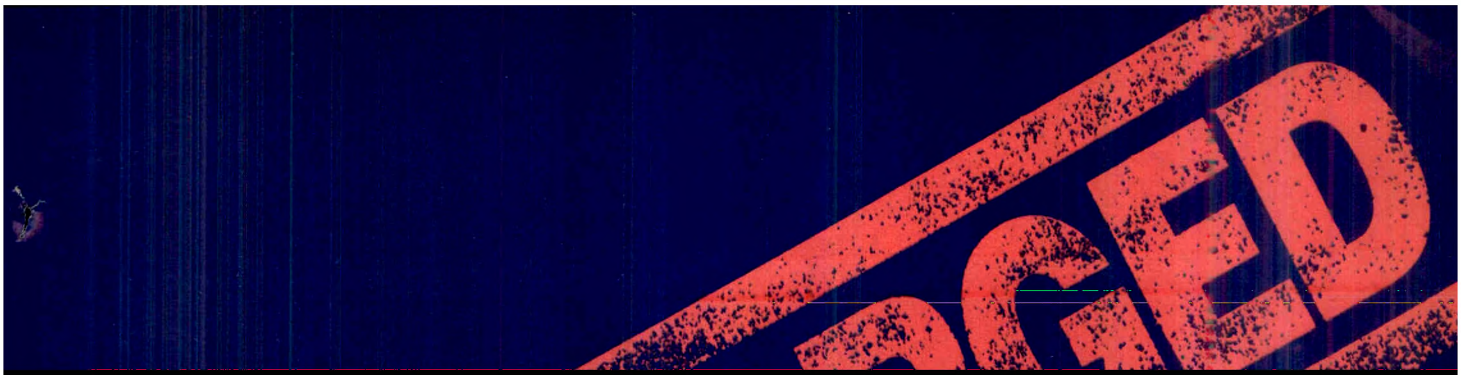
GED

A SUCCESSFUL TREATMENT OUTCOME FOR MANY PATIENTS*

INTRAVENOUS

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Meeting the surgical challenge:

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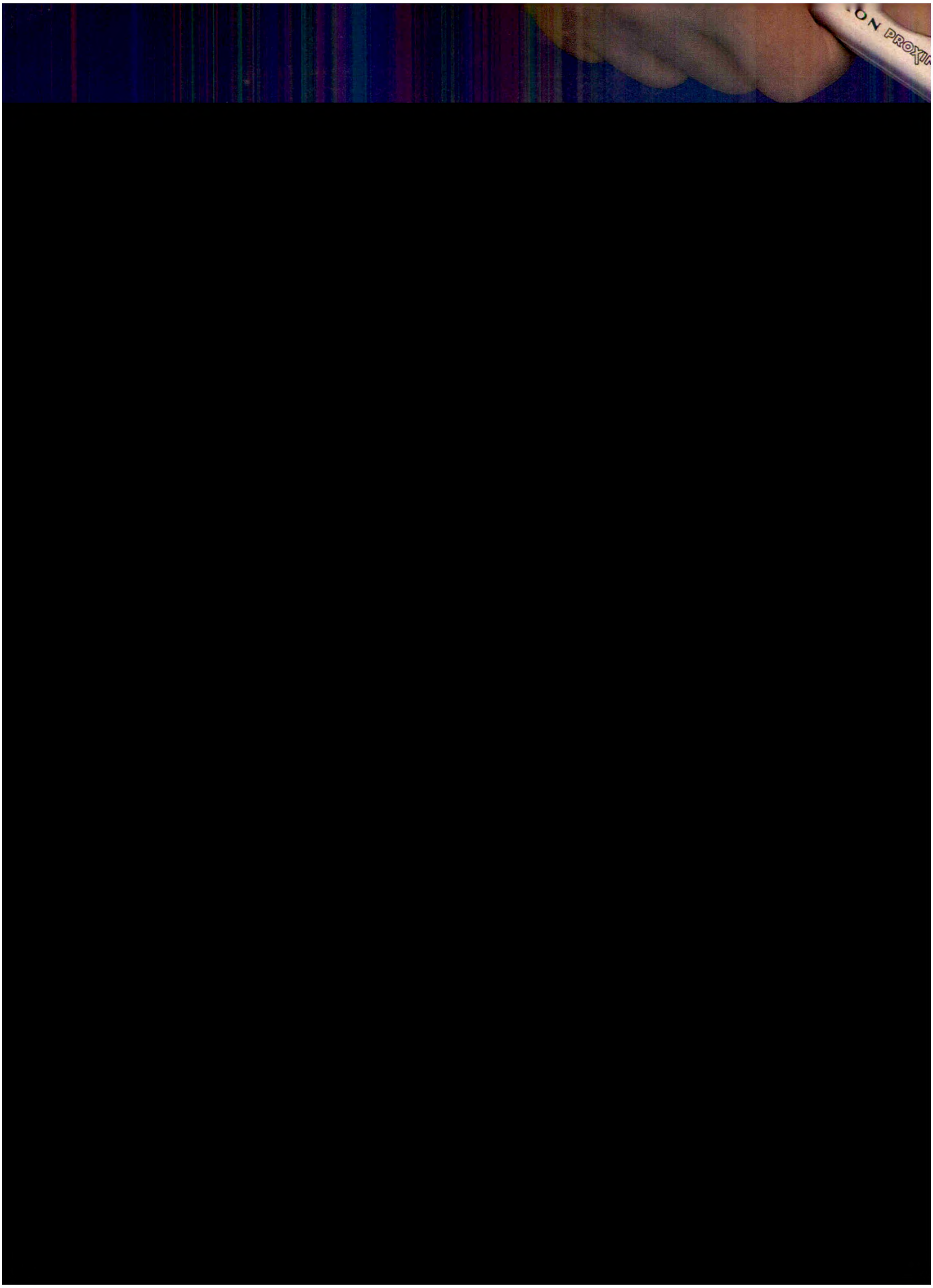
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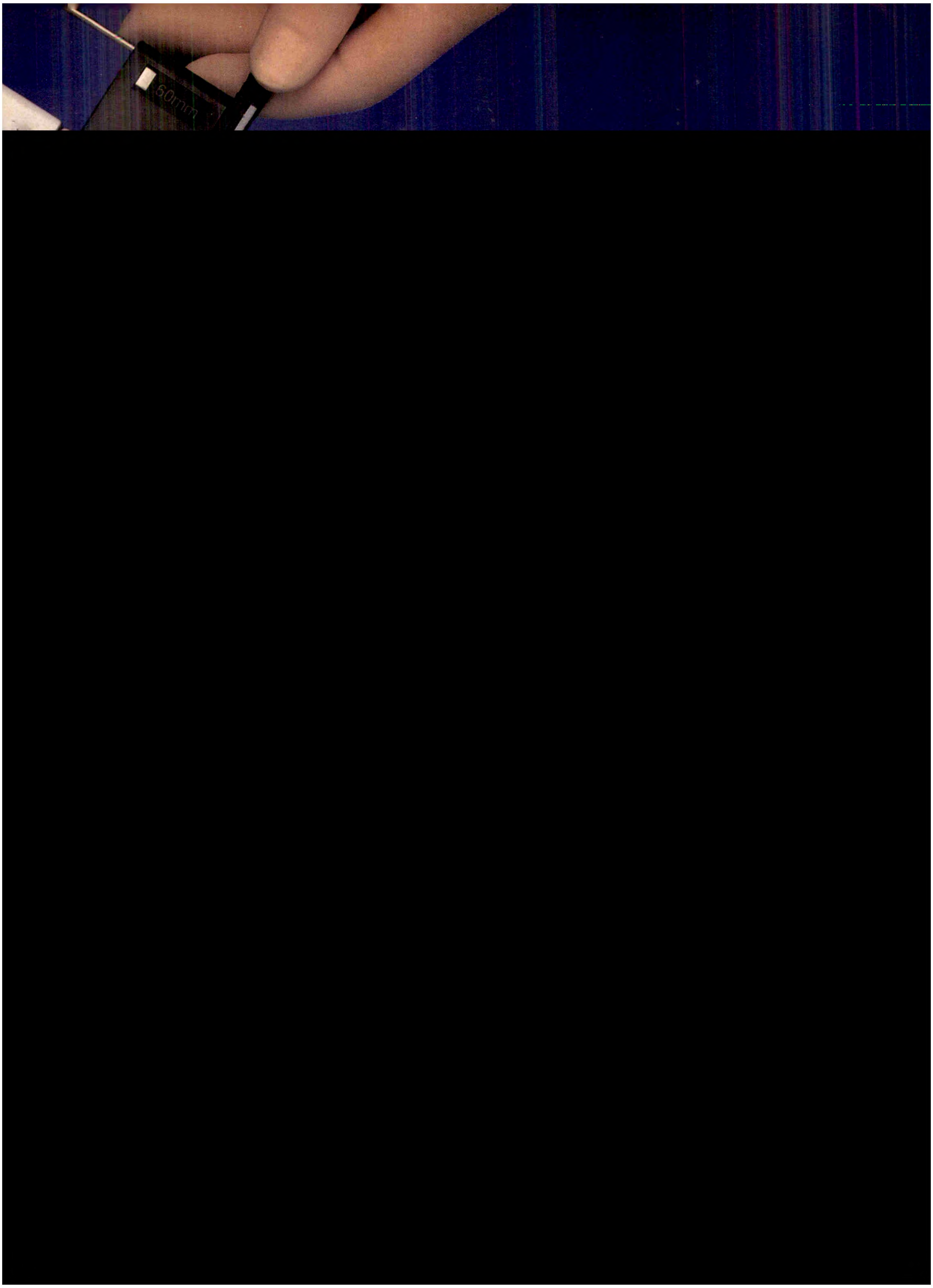
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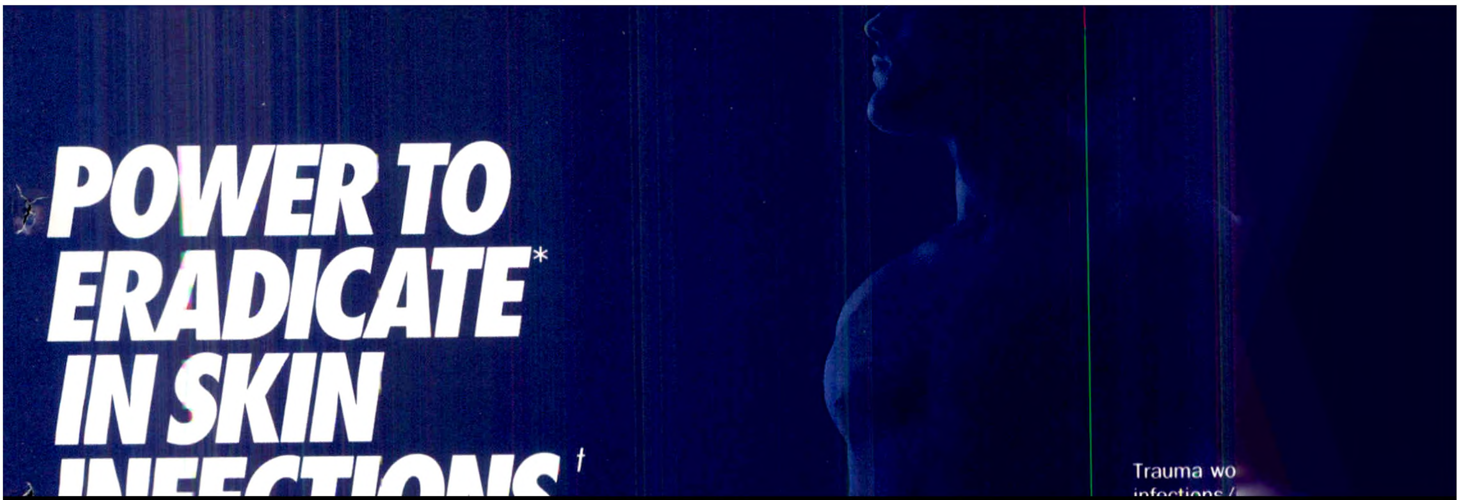
POWER TO
ERADICATE*
IN SKIN
INFECTIONS†
Trauma wo
infections

[redacted]

Cipro® TABLETS

(ciprofloxacin HCl/Miles)

POWER TO ERADICATE* IN SKIN INFECTIONS.

[redacted]

Papers Read Before the 97th Annual Meeting of the Western Surgical Association, St Louis, Mo,

[redacted]

areas of surgical intervention. Our instruments also are changing. Surgical involvement in endoscopic techniques will continue to receive strong interest. The surgeon will probably not discard the knives and scissors, but the various lasers and ultrasonic and dilating devices will continue to be tested for a permanent niche in our armamentarium. Implant, transplant, and reconstructive surgery probably will begin to predominate over extirpative surgery.

COMPETITION

The competition in many environments will shape the responsibilities of surgical practice. Fragmentation of general surgery into subspecialties such as vascular, critical care, and hand, which are currently certified, and fellowships in surgical oncology, transplantation, trauma, endocrine, and head and neck will continue to erode the corpus of general surgery. This erosion will be particularly dominant in the tertiary care

It embodies a strong basic science background so that the fledgling surgeon can come to understand all those disease processes in which surgical involvement and management are appropriate. We believe it is important to train the surgeon in the diagnosis of all surgical diseases and to confer skills in the use of endoscopes and the interpretation of roentgenograms, plain, contrast, and computed tomography, and in nuclear medicine and magnetic resonance images. We think the surgeon should be responsible for the preoperative preparation of the patient with regard to nutritional status, antibiotic usage, and the timing of the surgical procedure. The surgeon should be skilled in the technical aspects of the procedure to be undertaken, which includes having sufficient judgment to know what operation to do in what patient. The surgeon should manage the patient postoperatively, whether the patient is in the intensive care unit on a respirator or back in his or her hospital room, and be responsible for the antibiotics to

[redacted]

because we think it is in the best interest of our patients in regard to both cost-effectiveness and quality of care. Therefore, it behooves us to devise a training program that will ensure that our residents are capable of fulfilling these broad responsibilities. It is important that our surgeon of tomorrow have a strong training in basic science to fulfill the responsibilities of caring for the patient's problems of nutrition, infection, and respiratory, endocrine, cardiac, and immunologic manifestations or complications of the disease process. It is important that the surgeon be trained in depth in the anatomy and pathology of the vital organs and tissues encompassed by general surgery—to include the head and neck, the chest and its contents, the abdomen and its contents, the soft tissues, the breast, and the extremities. It is important that the surgeon be trained in the broadest aspects of cancer, transplantation, trauma, vascular, and gastrointestinal patho-

mies. This translates into approximately one operation of each of these types per resident. If we were to reduce the number of senior residents doing these cases by 40%, we would have an average of two of each of these procedures per resident, which is marginal to train surgeons to carry out each of these particular operations. When we look at radical extremity excision of soft-tissue sarcomas, major lymph node dissections, or choledochoenteric anastomoses, we see that the total numbers permit between two and four such operations per resident currently. We would increase that number to three to seven if we reduce the senior resident complement by 40%. It is clear that there is no shortage of sufficient vascular cases to train both specialists in vascular surgery and general surgeons. The abdominal aortic aneurysms reported by the general surgical residents average 7.8 and carotid endarterectomies 8.5 per resident.

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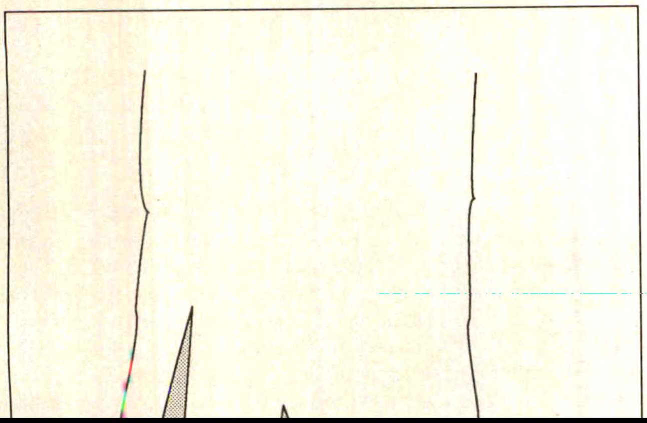

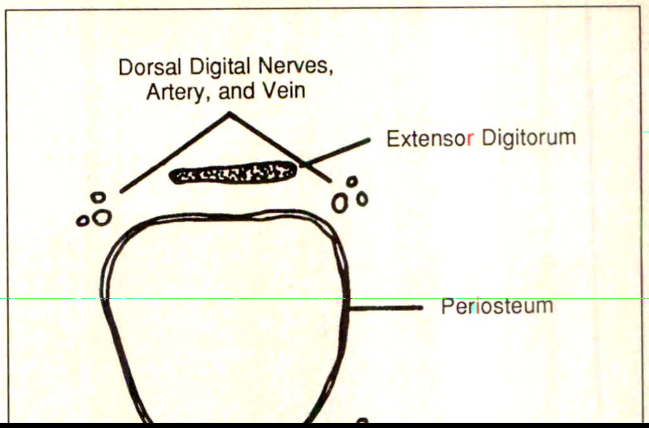
Dorsal Digital Nerves, Artery, and Vein
Extensor Digitorum
Periosteum

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References

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Table 1.—Age, y, of Patients

	Nonoperative Group		Operative Group	
	M (N=19)	F (N=15)	M (N=9)	F (N=8)
Mean ± SD	39.5 ± 21.8	46.3 ± 17.2	37.1 ± 15.2	54.4 ± 12.3
Median	29	44	35	54
Range	18-86	20-74	20-68	36-71

Table 2.—Mechanism of Injury

Table 3.—Associated Injuries

	Nonoperative Group	Operative Group
Rib fracture	16	10
Long bone fracture	6	9
Pelvic fracture	5	6
Hemopneumothorax	5	5
Lung contusion	4	11
Central nervous system	3	3
Neck	1	3
Urinary tract	1	3

[redacted]

colleagues of the validity of the approach, we were able to treat two thirds of our patients successfully without operation in the last 5 years, thus preserving splenic function in 68.6% (35) of our patients. Retrospectively, we reviewed the CT scans of the present series and classified them according to the system of Buntain et al,[12] who suggested that such a classification might be helpful in operative decision making. They suggested that patients with severe class 2 injury and all class 3 injuries should undergo early operation. Our retrospective review of 26 CT scans in the nonoperative group, however, identified 12 patients with class 2 injuries and 5 patients with class 3 injuries, all of whom were treated successfully without operative intervention. This finding tends to refute the value of the classification system.

At the present time, we believe that the hemodynamically stable, bluntly injured adult patient who has a ruptured spleen documented by CT scan and who has no other indications of other significant injury requiring immediate surgical intervention may be treated nonoperatively. If this course is chosen, it is imperative that the patients (1) be initially assessed and treated by a surgical team, (2) be admitted to an appropriate surgical critical care unit, (3) remain in a hemodynamically stable condition and do not require excessive blood transfusions (at present, >3 U is considered excessive), and (4) be closely observed for associated injuries and have proper treatment provided. In our hands, this has resulted in successful preservation of functioning splenic tissue in two thirds of the adult patients with blunt splenic injuries.

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on people with ruptured spleens. They are recommending that you

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The Management of Splenic Trauma in a Trauma System

[redacted]

Table 1.—Splenic Injury Scale*

Grade†		Injury Description‡	*ICD-9*	AIS 85	AIS 90
I	Hematoma	Subcapsular, nonexpanding, <10% surface area	865.11	2	2
	Laceration	Capsular tear, nonbleeding, <1-cm parenchymal			

[redacted]

Table 4.—Comparison of the Level I Center With the Level II Centers*

Level	TS	ISS	Ps	TX	Major Septic Complications, %	Salvage, %	Receipt of Pneumococcus Vaccine, %†
I (N=117)	13±1	29±1	.84±.02	2.8±0.3	29	50	53
II (N=311)	13±1	29±1	.84±.02	2.5±0.3	19	38	74

*TS indicates trauma score; ISS, injury severity score; Ps, probability of survival; and TX, average units of blood per patient.
†$P<.05$ by χ^2.

COMMENT

Numerous reports have documented the experiences of single trauma centers in the management of splenic injury.[9-15,21] This review is the first to document the experience of a single trauma system in the treatment of splenic injury

[redacted]

have been a function of the fact that there were fewer trauma surgeons, thus more experience with splenorrhaphy per surgeon. The observation that the salvage rate improved over the 4 years of study supports the hypothesis that experience is important in successful splenorrhaphy. The higher compli-

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Table 4.—Factors Affecting Length of Hospitalization for All Patients Sustaining Truncal Stab Wounds

Variable	No. of Patients	Hospitalization, d
All stab wounds	1241	7
Positive celiotomy	770	8
Negative celiotomy	471	5
Associated operations	34	9
Postoperative complications	16	16
Reoperation	4	27
Death	1	39

Table 5.—Average Hospital and Physician Charges for Negative Exploratory Celiotomy During a 10-Year Period

Year	Hospital Charges, $US	Physician Charges, $US	Total, $US
1981	2106	1874	**3980**
1984	2759	1684	**4443**
1987	4070	1910	**5980**
1990*	5415	2210	**7625**
Percent rise in 10 y	157	18	92

*Projected.

by tenderness, rebound tenderness, abdominal wall spasm, and/or reduced or absent peristalsis) would then undergo an exploratory operation.[2] His prospective study using this protocol for 180 patients showed that the negative celiotomy rate could be reduced to 7% and that 69% of the patients could be treated without an operation.

Nance and Cohn,[3] in 1969, became proponents of "selective conservatism" for patients with abdominal stab wounds. Their report documented how one examiner could become proficient in selecting a group of patients who could be safely observed. A subsequent report from their institution documented the ability of surgical house officers to reliably identify those patients with stab wounds who required exploration.[19] A 10-year retrospective study of 219 patients treated by Nance and Cohn's protocol appeared in 1983.[20] Based on physical examination as the only routine diagnostic procedure, 111 patients were treated nonoperatively, 90 patients underwent immediate exploratory celiotomy, 18 patients were observed initially and then underwent exploration, and 1 patient not operated on, who had had clear-cut indications for operation, died of sepsis. Their negative celiotomy rate was 7.8%; the false-negative examination rate, 5.5%; and overall mortality rate, 2.3%.

Despite these encouraging results, other surgeons have

percent of those patients without an intra-abdominal injury at exploration developed postoperative complications. There were no postoperative deaths. Oreskovich and Carrico[20] compared the quantitative peritoneal lavage results (cell counts) with the incidence of injury in patients with stab wounds to the anterior aspect of the abdomen. Ninety-two percent of patients with red blood cell lavage counts greater than .05 × 10¹²/L had sustained an intraperitoneal organ injury. In contrast, no patients with lavage counts less than .001 × 10¹²/L red blood cells had an organ injury. They discovered a visceral injury in 48% of patients in the intermediate group (red blood cell count of .001 to .05 × 10/¹²L), 59% of whom had penetration of a hollow viscus. They contended that exploratory celiotomy following local wound exploration and quantitative peritoneal lavage should yield a negative celiotomy at laparotomy in less than 10% of the patients.

Opponents of the concept of peritoneal lavage in patients with truncal stab wounds contend that the procedure is both time-consuming and costly.[1] Additional substantive objections include the following: (1) missed and iatrogenic injuries are inherent in the procedure itself, (2) there is questionable value in the diagnosis of diaphragmatic injuries and isolated bowel perforation,[8-10] and (3) the procedure has no role in evaluating patients with stab wounds to the back and

[redacted]

Table 6.—Estimated Observation Charges*

	Cost, $US

was initiated to document the results of such a policy. In addition, we desired to ascertain whether a new therapeutic approach was warranted after assessing the risk-to-benefit ratio. Finally, in the era of diagnosis related groups, rising

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urgent tracheostomy for airway control was statistically asso- [redacted]

choice if endotracheal intubation cannot be accomplished.[13,14]

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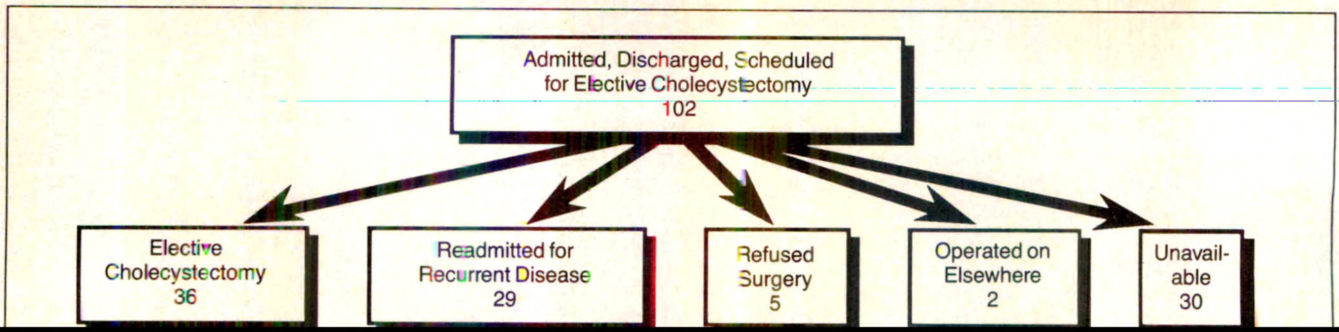
Admitted, Discharged, Scheduled for Elective Cholecystectomy 102
Elective Cholecystectomy 36
Readmitted for Recurrent Disease 29
Refused Surgery 5
Operated on Elsewhere 2
Unavail-able 30

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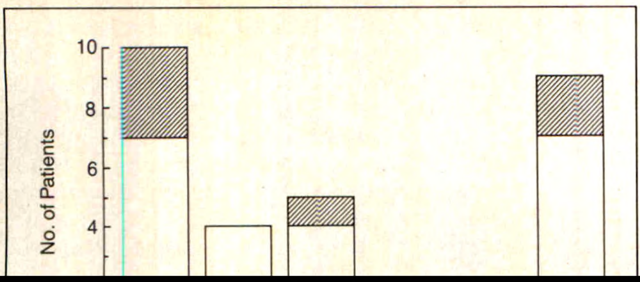
No. of Patients
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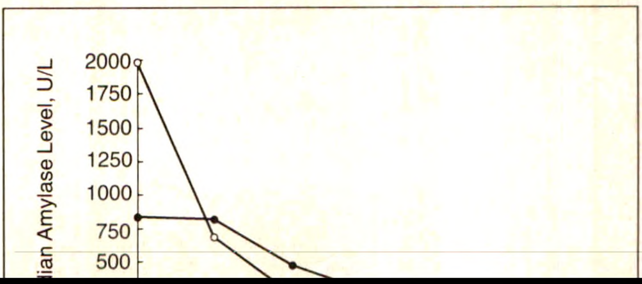
dian Amylase Level, U/L
2000
1750
1500
1250
1000
750
500

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biliary surgery be performed after complete recovery from the illness. This approach was generally accepted even though, in 1962, Howard and Ehrlich[9] acknowledged that "many" patients could undergo surgery soon after the symptoms subsided. They nevertheless advocated a conservative approach since they had seen patients progress from edematous pancreatitis to HNP after surgery. In 1967, White and Murat[24] urged caution when performing biliary surgery in patients with pancreatitis. They recommended that the sphincter of Oddi not be dilated beyond 6 mm and that long-armed T-tubes not be placed through the papilla of Vater. Vigorous dilatation of the sphincter or the use of long-armed T-tubes often resulted in the death of the patient.

In view of the conservative atmosphere of the 1950s and 1960s, it is not surprising that surgeons were reluctant to operate on patients during the same admission. However, concern about the high risk of recurrence provided the stimulus for change. In 1974, Kelly[25] began to advocate same-admission surgery. In 1975, Paloyan et al[10] demonstrated the safety of same-admission surgery after resolution of the acute attack by operating on 29 patients in this condition, without a death. More remarkably, 16 additional patients underwent surgery because their conditions failed to improve or deteriorated, and all 16 survived. At the present time, most authorities recommend same-admission surgery after the subsidence of symptoms.[5,7,8,20,21,26,27]

Acosta et al[8] reported a unique experience from Argentina in 1978. Like others, they noted that most patients recovered quickly with medical therapy and could be operated on electively. Unfortunately, a greater proportion of their patients (24% [21/86]) had deteriorating conditions and required emer-

cholecystectomy and common duct exploration if indicated, they operated on 34 consecutive patients within 48 hours of admission. Twelve patients (35%) had common duct stones, and 4 of these patients (12%) had impacted stones. No patients with HNP were encountered, and no patients died. They concluded that cholecystectomy and common duct evaluation or exploration were safe and sufficient treatment when performed with 48 hours of admission.

In contrast, many authors have reported poor results with early surgery. Ranson[5] published the results of a study in 1979 that compared patients operated on early (median of 2 days after admission) with those operated on late (> 7 days after admission but during the same hospitalization). In the early group, 4 (23%) of 22 patients had HNP, and 5 (23%) died; in the late group, 2 of 37 patients had hemorrhagic fluid on paracentesis (implying HNP), but none died. Ranson concluded that early surgery was hazardous in patients with "severe disease" (prognostic score, ≥3, which included the 4 patients with documented HNP). He recommended that biliary surgery in these patients be deferred until the acute process resolved.

In 1980, Kelly[6] reported on a study in which 24 patients were operated on within 72 hours of admission because their conditions failed to improve. An additional 148 patients were operated on after recovery. In the emergency group, 4 patients had HNP, and three (13%) died. In the patients whose conditions improved, none had HNP, and only 1 (1%) died. Kelly concluded that early surgery should be performed only in those few who do not recover promptly. For the majority of patients, he recommended surgery after clinical recovery because of its safety.

NEW

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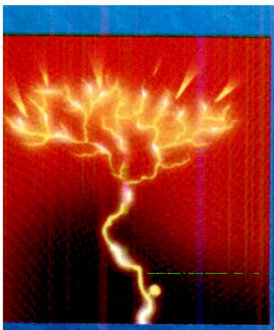

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AND OTHER
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The first peripherally acting analgesic with efficacy comparable to morphine 12 mg and meperidine 100 mg

Analgesic efficacy of TORADOL IM administered 24–72 hours postsurgery[1]

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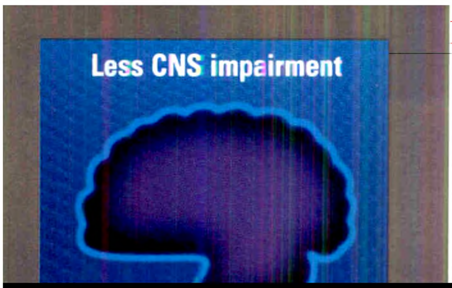

START RECUPERATION WITHOUT NARCOTIC SIDE EFFECTS[1*]

[redacted]

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- Does not act on opiate receptor sites
- No potential for abuse

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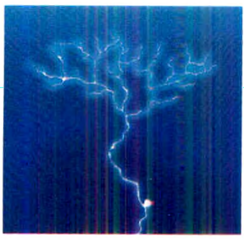

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PROPER DOSAGE POSTOPERATIVELY

For maximum analgesia:

- Give patients prompt pain relief: start with loading dose of 60 mg IM
- Follow with maintenance dose of 30 mg IM Q6h to control pain
- The recommended maximum total daily dose is 150 mg for the first day and 120 mg/day thereafter*

Simulated incremental plasma concentrations after

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TORADOL® IM (ketorolac tromethamine)

Brief Summary

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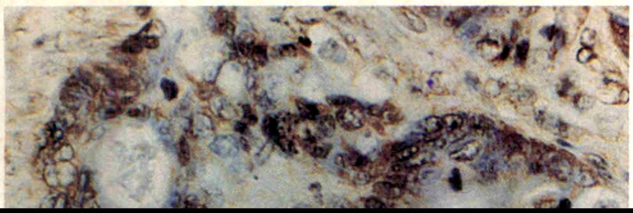

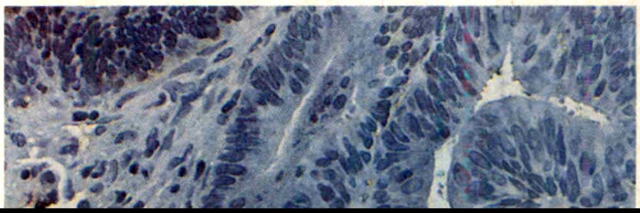

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Radioimmune Localization of Occult Carcinoma

Rosemary B. Duda, MD; A. Michael Zimmer, PhD; Steven T. Rosen, MD; Katherine A. Gilyon, RN;
Denise Webber; Stewart Spies, MD; William Spies, MD; Bruce Merchant, MD, PhD

• Patients with a rising serum carcinoembryonic antigen level and no clinical or roentgenographic evidence of recurrent or metastatic cancer present a treatment dilemma. Eleven such patients, 10 with a previously treated colorectal carcinoma and 1 with a previously treated breast carcinoma, received an injection of the anticarcinoembryonic antigen monoclonal antibody ZCE-025 labeled with the radioisotope indium 111. Nuclear scintigraphy was performed on days 3 and 5 through 7 to detect potential sites of tumor recurrence. The monoclonal antibody scan accurately predicted the presence or absence of occult malignancy in 7 (64%) patients. Second-look laparotomy confirmed the monoclonal antibody scan results in the patients with colorectal can-

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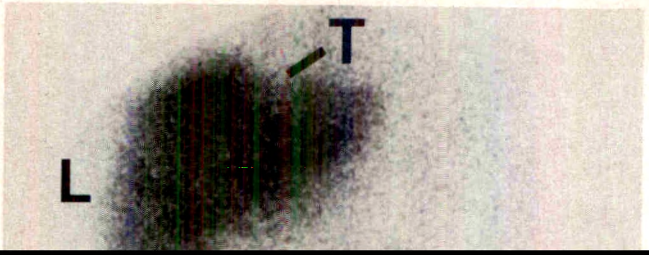
PATIENTS AND METHODS

ZCE-025 is a murine IgG1 MAB that has a high affinity for the CEA and does not cross-react with granulocyte glycoproteins.[13,14] This antibody has been demonstrated to successfully localize colon cancer xenografts in nude mice[15] and colorectal carcinoma in human patients.[8] The ZCE-025 was provided by Hybritech Inc, San Diego, Calif, in a kit that included the antibody, neutralizing buffer solution, and indium 111–citrate in sterile, nonpyrogenic preparations. All patients received 40 mg of antibody labeled with 185 MBq of indium 111 in 48 mL of normal saline by slow intravenous infusion. The ZCE-025 MAB is approved by the Food and Drug Administration (Wash-



tion analysis of radioactive antibody content. The average uptake in the normal liver tissue of these three patients was 14.18 ± 1.1 (%ID/kg). Only two patients had hepatic metastasis available for tissue biodistribution studies. The average uptake of the rim of a hepatic metastasis was 10.20 ± 1.2 %ID/kg and the average uptake of the core of the hepatic metastasis was 10.72 ± 4.0 %ID/kg(Table).

The mean ± SE serum CEA level for all patients with a true-positive MAB scan was 53.4 ± 20 ng/mL. The patient

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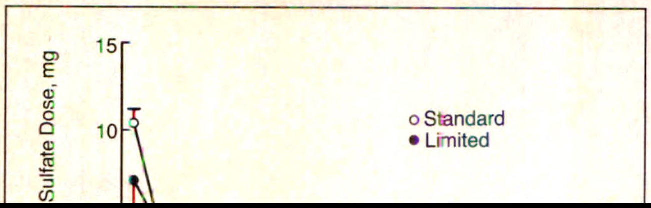


dorsi was described as early as 1952 by Browne[7] and has been used by others for the transaxillary approach to the thoracic cavity.[8,9] We modified this with an anterior extension below the breast, which appears to improve exposure and allow better retraction of the serratus anterior. In our view, however, the direction of the skin incision is less important than preservation of the major muscle groups, in particular the

[redacted]

hospital stay difficult. Although we did not measure postoperative mobility of the upper limb on the operated-on side, it was our impression that functional disability was less in the LTD group. Accordingly, we are planning to study in the future the effects of these incisions on recovery of upper-extremity function.

In summary, this prospective randomized controlled study demonstrated that the use of an LTD incision resulted in improved early postoperative spirometric test volumes re-

[redacted]

increased by this more limited approach, and, was the operation more difficult in the experience of the surgeon?

Alan R. Hopeman, MD, Denver, Colo: I have some concerns about this paper. I use this incision a lot, and I like it for some cases, but I do have some concerns about training residents in this technique because sometimes you just need a little more space. I am also concerned that this incision is not readily extended, as the STD is, for work at the hilum for central lesions.

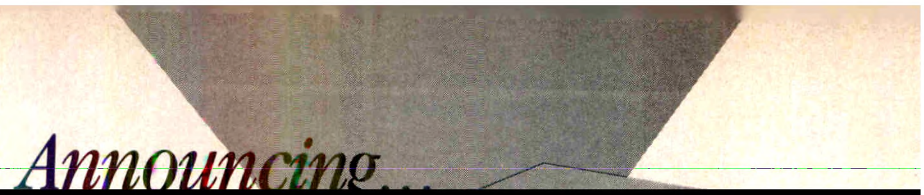
I also wonder why pneumonectomies were eliminated from this study.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

TIMENTIN® **sterile ticarcillin disodium and clavulanate potassium** for Intravenous Administration

INDICATIONS AND USAGE: TIMENTIN® is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Bacterial Septicemia: including bacteremia, caused by β-lactamase producing strains of *Klebsiella* spp., *E. coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* (and other *Pseudomonas* species). Lower Respiratory Infections: caused by β-lactamase producing strains of *Staphylococcus aureus*, *Hemophilus influenzae*, and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years. The majority of recipients (15 patients) were dialysis dependent while 2 patients underwent transplantation prior to the need for dialytic therapy. One of the latter patients was rapidly losing function [redacted]

Table 1.—Patient Population (N = 17)

Sex distribution	
[redacted]	[redacted]

Table 2.—Kidney and Pancreas Function Following Simultaneous Transplantation

	No. of Months After Transplantation, Mean ± SD					
Factors Studied	**1 (n=17)***	**3 (n=17)**	**6 (n=16)**	**12 (n=9)**	**18 (n=5)**	**24 (n=4)**
Creatinine, μmol/L	186 ± 71	150 ± 42	159 ± 62	177 ± 71	133 ± 35	106 ± 71
Glucose, mmol/L	4.5 ± 0.5	4.8 ± 1.2	4.8 ± 0.8	4.9 ± 1.0	4.2 ± 1.1	5.3 ± 0.8
Glycohemoglobin, %†	6.3 ± 2.0	5.0 ± 0.9	5.4 ± 1.3	5.4 ± 0.4	5.4 ± 0.8	5.3 ± 0.7

*Numbers in parentheses indicate number of patients observed.

[redacted]

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The Importance of DNA Flow Cytometry in Node-Negative Breast Cancer

[redacted]

remove subcellular debris. One milliliter of a modified Hedley buffer (prepared with 250 mL of distilled water, 1.211 g of TRIS hydrochloride, 0.2541 g of magnesium chloride, 0.75 mL of NP 40 detergent (Sigma Chemical Co), at a pH adjusted to 7.0 with hydrochloric acid, and 0.0125 g of propidium iodine) with 1 mg/mL of RNAse (Worthington Biochemical, Freehold, NJ) was used to incubate at 37°C for 30 minutes in a light-sealed incubator. Samples were centrifuged and resuspended with 1.0 mL of the modified Hedley solution to stain overnight at 4°C. Before analysis, each sample was propelled through a 28-gauge insulin syringe three times to ensure a single-cell

Table 1.—Generalized Wilcoxon Univariate Survival Analysis for All Patients (N = 198)

Variable	Recurrence, *P* Value	Cancer Death, *P* Value
Tumor diameter	.001	.001
Histologic grade	.002	.02
Nuclear grade	.008	NS*
Mitotic grade	NS	.04

[redacted]

bined with conventional clinical factors, can be an important predictor of early relapse. This distinction may be useful in making treatment decisions for women with node-negative breast cancer and requires further prospective analysis.

This investigation was supported by the Alyce Salerno Foundation, Chicago,

whether we should subject patients with node-negative cancer to chemotherapy. My only caution is that these are early days, too, and I keep wondering whether the diploid/aneuploid story may go the way of the receptor story. While I think that what you have told us is very encouraging, I would not as yet bet on this as a solution to our therapeutic dilemmas that will necessarily stand the test of time.

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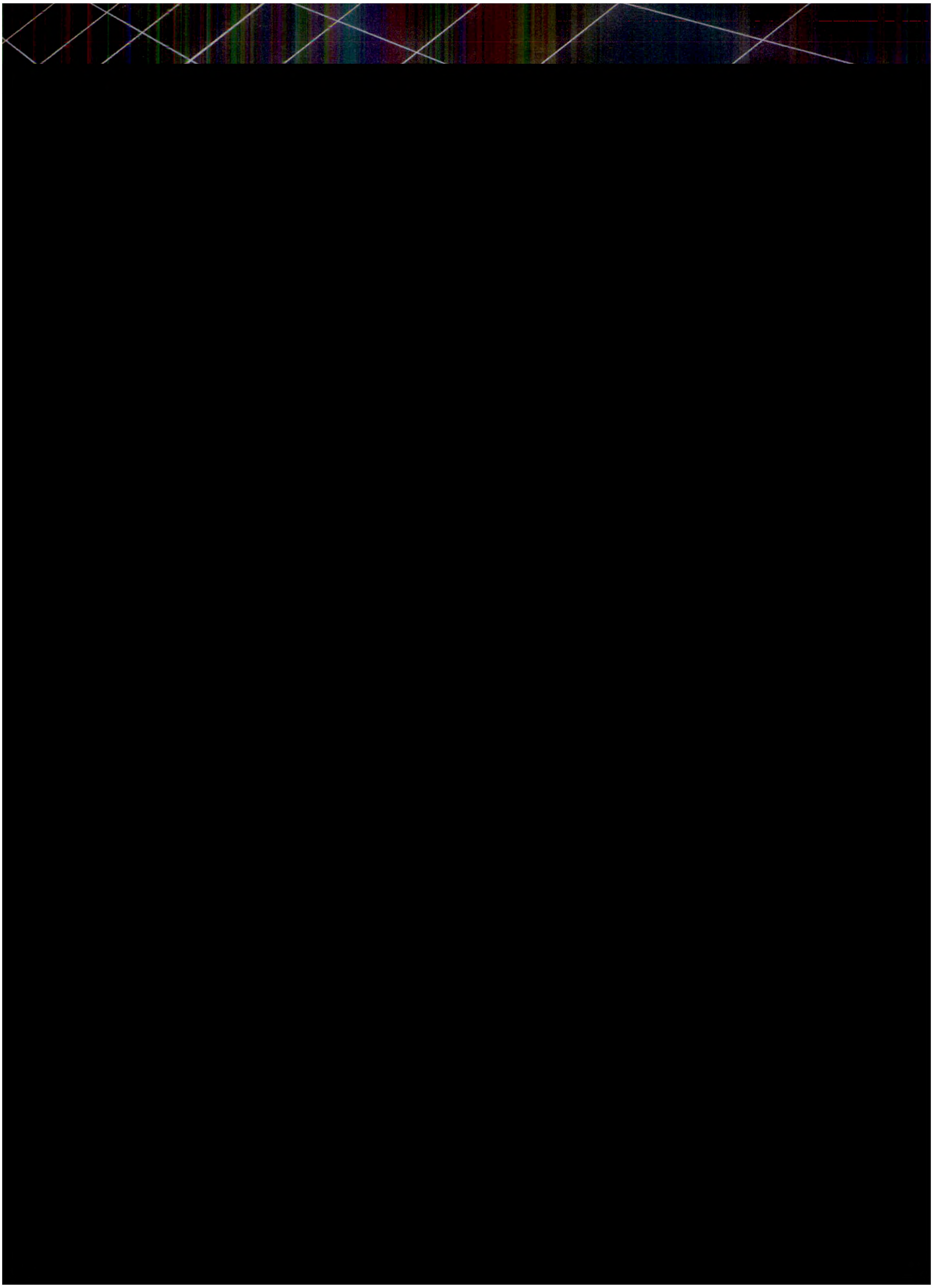

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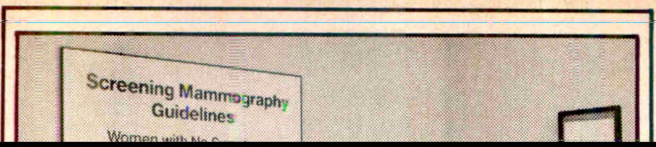

Screening Mammography Guidelines

Women with No

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negative predictive values were determined for each technique. The correlation of the histologic diagnosis with the combined results of the three preoperative examinations was also examined.

RESULTS

The median age of the 113 patients was 45 years, with a range from 30 to 76 years. Sixty-four of the patients were premenopausal and 49 were postmenopausal. Twenty-five of the patients (22%) had a history of prior breast surgery, 17 for benign disease and 8 for cancer. The median size of the dominant masses on the basis of the clinical examination was

Table 1.—Histologic Findings of 113 Breast Biopsy Specimens

Type of Lesion	No. of Biopsy Specimens
Malignant	
Infiltrating ductal	49
Lobular	1
Medullary	1
Papillary	1
Total	**52**
Benign	
Fibrocystic changes	[illegible]

[redacted]

Table 3.—Validity of the Individual Diagnostic Tests

	n	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Negative Predictive Value, %
Physical examination	113	96	66	70	95
Mammography	86	84	73	71	85
Fine-needle aspiration cytologic examination	113	90	93	92	92

Table 4.—Correlation of the Diagnostic Triad With Final Histologic Findings

Suspicious/Malignant Test Results	Histologic Findings, No. (%) of Patients	
	Benign	Malignant
0	25 (52)	0 (0)
1	17 (36)	1 (3)
2	5 (10)	9 (24)
3	1 (2)	28 (73)

preoperative test in that it provides a tissue diagnosis with a

Our results with the triple test support the findings of Hermansen et al. The 25 masses recorded as benign on the three examinations all proved to be benign on final histologic examination. This represented 52% of all benign biopsies performed on the 86 patients who underwent the triple test. Only 1 (6%) of 18 patients with a single suspicious/malignant result had cancer. Twenty-eight (97%) of 29 patients with three suspicious/malignant results had a cancer. The one patient in that group with a benign lesion had an aspirate that was suspicious for malignancy. The specificity for masses labeled as clearly malignant was 100% on the basis of no false-positive aspiration cytologic study results.

Two caveats must be emphasized in interpreting these findings. Our patient population was largely indigent; their presentation may differ considerably from that of patients

[redacted]

Discussion

ARMANDO E. GIULIANO, MD, Los Angeles, Calif: More than 500 000 breast masses are excised annually in the United States. A protocol to reduce the number of biopsies without lowering the detection of cancer would be welcome. Dr Butler and coworkers nicely report the results of using three common, nonoperative, diagnostic techniques for the management of palpable masses. By combining palpation, mammography, and fine-needle aspiration cytologic examination, the triple protocol, this study shows that if all three test results are interpreted as suspicious or malignant, the likelihood of the patient's having breast cancer is 97%.

With discordant results among the three studies, the probability of encountering a malignant neoplasm decreases. Most important, since the purpose of this study was to identify a subset of patients who could be safely observed, all of the 25 patients in whom the triplet was benign had a benign lesion on permanent histologic section.

The finding of the predictive power of a negative triplet is not unusual in the literature, although, as the authors suggest, their 100% accuracy for benign lesions may reflect the small size of that group. At the UCLA Center for the Health Sciences we found one malignant neoplasm among 47 negative diagnostic triplets. The incidence in the literature of false-negative triplets is around 2% to 4% in experienced hands.

Many authors, including those in the present study, support the

M. MICHAEL SHABOT, MD, Los Angeles: In 1982 Yosef Pilch and I reported on a similar group of patients from the same clinic; our diagnostic accuracy rate for fine-needle aspiration was 96.2%. We were working with a very talented cytopathologist. When I left that institution the cytopathologist left as well, and I note that the diagnostic rate for fine-needle aspiration is now somewhat different.

My concern is translating the authors' results to the institutions we all represent; how do we know how well our own cytopathologists are performing? Clearly, the diagnostic accuracy of this diagnostic triad is heavily dependent on the cytopathologist. I'm concerned that this study showed false-negative results in each aspect of the triad. If three false-negative results occurred in one patient, an overall false-negative diagnosis would result.

JACK PICKLEMAN, MD, Maywood, Ill: Even if the false-negative rate using all three criteria is 1%, 2%, or 3%, that is unacceptably high. I've spent half my professional life trying to teach medical students that all dominant breast masses have to undergo biopsy and cannot be safely observed, for the reasons we've discussed here today. Now, along comes this report saying that that's not true. I am very disheartened to hear this message that we should pass on to our future family practitioners.

J. BRADLEY AUST, MD, San Antonio, Tex: I have a problem with the logic involved. The logic sequence is really not a triplet, but,

[redacted]

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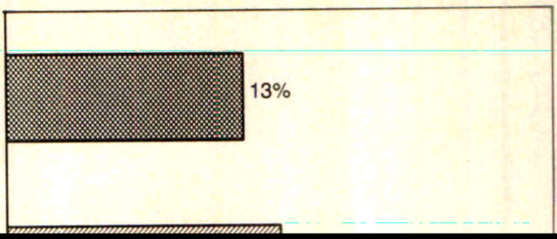
Table 3.—Postoperative Complications According to Treatment Arm*

Complication	Control	Portal Vein Infusion
Urinary retention	4	3
Wound infection	3	2



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Zinacef®
(sterile cefuroxime sodium, Glaxo)

Zinacef®
(cefuroxime sodium injection)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zinacef® product labeling.

INDICATIONS AND USAGE: Zinacef® is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

1. **Lower Respiratory Tract Infections,** including pneumonia, caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* spp, *Staphylococcus aureus* (penicillinase- and non-penicillinase producing), *Streptococcus pyogenes*, and *Escherichia coli*.
2. **Urinary Tract Infections** caused by *E coli* and *Klebsiella* spp.
3. **Skin and Skin Structure Infections** caused by *S aureus* (penicillinase- and non-penicillinase-producing), *S pyogenes*, *E coli*, *Klebsiella* spp, and *Enterobacter* spp.
4. **Septicemia** caused by *S aureus* (penicillinase- and non-penicillinase-producing), *S pneumoniae*, *E coli*, *H influenzae*

Journals
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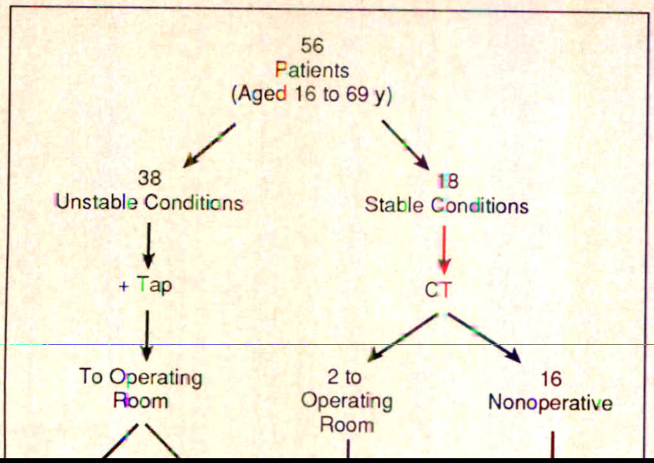

Table 1.—Injury Severity Scores and Blood Transfusions*

Injury Severity Score	No. of Nonoperative Patients (n = 16)	No. of Operative Patients (n = 40)
<10	2	0
10-20	4	4
21-30	7	8
31-40	3	9
41-50	0	17
51-60	0	1
>60	0	1

*The mean injury severity score was 23.9 for nonoperative patients and 36.7 for operative patients ($P<.001$). The mean number of units of red blood cell transfusions was 1.2 for nonoperative patients and 6.9 for operative patients ($P<.001$).

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In choosing
a graduate program...

Rely on these
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disease is assessed initially. Presence of metastatic disease would be a contraindication to performing sacral resection. Then the tumor is dissected free from the pelvic structures, which include the ureters, bladder, and, in the case of rectum-sparing procedures, the rectum. The small bowel is packed in the peritoneal cavity away from the pelvis. Fecal and urinary diversions are then performed as indicated.

Through a separate intergluteal incision, the sacrum is exposed. The ligamentous attachments of the sacrum to the rest of the pelvis

Table 2.—Operative Data*

	Group A	Group B	Combined
Operative mortality	0	0	0
Operative time, h (median)	5.5	5	5.5
Blood loss, mL (median)	1500†	1400	1600

[redacted]

wound disruption were the two major complications. Urinary incontinence occurred in three patients. Both cases of wound disruption occurred in patients who had received radiotherapy to the tumor preoperatively. Radiotherapy should not be used for chordomas, as these tumors are not radiosensitive.

Locally Invasive Rectal Cancers

Patients with symptomatic recurrence of invasive anorectal cancer involving the sacrum with no evidence of metastatic disease are candidates for this operation. The decision is made after a thorough discussion of therapeutic options with the patient. Obviously, the final decision to perform the resection depends on the intraoperative findings of local and distant extent of the disease. We have not found disease-free interval from the time of initial surgery to be a useful predictor of postoperative recurrence of disease.

Reports of sacral resection for locally invasive rectal cancers are few.[4,6] The most extensive report is by Wanebo and coworkers.[6] In their series, 28 patients underwent resection of recurrent rectal cancer. Even though their end results are comparable with ours in terms of 1- and 2-year disease-free survivals, their operation itself was truly heroic. Median blood loss was reported at 6000 mL, median operative time

[redacted]

were unavailable for follow-up after 8 months, while another patient has no evidence of disease 7 months postoperatively. Despite the discouraging survival rates, palliation was significant: all patients had excellent relief of their preoperative pain following the operation. Return of pain usually signaled local recurrence.

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Acute Ileus From Steroid Withdrawal Simulating Intestinal Obstruction After Surgery for Ulcerative Colitis

Matthias Stelzner, MD; J. Duncan Phillips, MD; Eric W. Fonkalsrud, MD

• Sixty of 127 prednisone-dependent patients with ulcerative colitis who underwent colectomy and endorectal ileal pullthrough with ileal reservoir and subsequent laparotomy with ileostomy closure (254 operations) during a 4-year period developed 95 episodes of intestinal obstruction during the early postoperative period. Acute ileus due to steroid withdrawal caused symptoms of intestinal obstruction in 43 patients (76 episodes), whereas true mechanical small-bowel obstruction occurred in only 17 patients (19 episodes). Symptoms of both conditions were similar; however, hypoactive bowel sounds, acute onset of emotional depression, no evidence of obstruction on radiologic contrast stomatogram or enema, and prompt relief of symptoms within 4 hours after intravenous administration of hydrocortisone acetate distinguished acute steroid withdrawal. Since ileus from acute steroid withdrawal occurred four times as frequently as mechanical small-bowel obstruction, prompt recognition and treatment should appreciably reduce postoperative morbidity and hospital costs.

(*Arch Surg*. 1990;125:914-917)

Gastrointestinal tract disturbances, including anorexia, nausea, emesis, diarrhea, and weight loss, occur in more than 50% of patients with adrenal insufficiency.[1] Approximately one third of patients with chronically decreased serum cortisol levels experience diarrhea or constipation. Acute adrenal insufficiency is often accompanied by emesis, abdominal pain, and occasional diarrhea as predominant symptoms, which may simulate an "acute abdomen."[2,3] Almost all patients with ulcerative colitis who undergo colectomy and endorectal ileal pullthrough operations with construction of an ileal reservoir (PTR) receive corticosteroids as part of their medical therapy during the months or years before surgery. Most of these patients require perioperative exogenous steroid replacement because of chronically suppressed adrenal function. During the early postoperative period, many will experience symptoms of acute ileus with abdominal distention, pain, nausea, and emesis, and in many cases emotional lability as the steroid dosage is reduced.

Small-bowel obstruction (SBO) due to adhesions has been reported to complicate the postoperative course in more than 10% of patients undergoing the PTR procedure.[4-7] The close resemblance between acute ileus associated with steroid withdrawal and mechanical SBO due to adhesions both clinically and radiologically renders the differential diagnosis especially difficult.

In the present study we report our experience with symptoms of intestinal obstruction due to steroid withdrawal in 43 of 127 consecutive patients with ulcerative colitis who underwent colectomy and the PTR procedure. A comparison is made with 17 of the 127 patients who developed true mechanical SBO requiring specific therapy.

PATIENTS AND METHODS

From 1984 through 1988, a total of 127 patients with ulcerative colitis underwent colectomy and the PTR procedure with temporary diverting ileostomy in two stages at UCLA Medical Center as described previously.[8] At the first operation, the colon and rectal mucosa were removed, a lateral ileal reservoir was constructed, and an endorectal ileal pullthrough with ileoanal anastomosis was performed. A temporary diverting end ileostomy was constructed in all patients. The second operation consisted of laparotomy with closure of the ileostomy.

All but two of the patients had received corticosteroids during the year before the first-stage operation and were therefore given perioperative hydrocortisone acetate before and after both of the scheduled operations. Two patients underwent the PTR procedure without steroid supplementation. The perioperative corticosteroid regimen consisted of three doses of hydrocortisone acetate (100 mg) at 8-hour intervals on the day of operation. Intravenous steroid doses were then tapered rapidly, and oral prednisone was started on the fourth day after the first operation and on the fifth day after the second-stage operation.

In a retrospective review of 127 consecutive patients with ulcerative colitis who underwent the PTR procedure at UCLA Medical Center (254 operations), 60 experienced symptoms of ileus or intestinal obstruction during the postoperative period. The 43 patients with

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From the Department of Surgery, UCLA School of Medicine.
Read before the Southern California Chapter of the American College of Surgeons meeting, Palm Springs, Calif, January 27, 1989.

Reprint requests to Department of Surgery, UCLA School of Medicine, Los Angeles, CA 90024 (Dr Fonkalsrud).

Acute Ileus From Steroid Withdrawal—Stelzner et al

[redacted]

tifying each of the two conditions. Both conditions are often characterized by abdominal pain, distention, nausea, emesis, decreased intestinal output, and similar appearance on abdominal roentgenograms. Early in its course, mechanical SBO is likely to produce active peristalsis with hyperactive bowel sounds, in contrast to the reduced bowel sounds related to steroid-withdrawal ileus. The combination of gastrointestinal tract symptoms together with acute psychological depression and a history of long-term steroid intake with rapid downward tapering should increase the awareness of possible acute steroid insufficiency. A radiologic contrast stomatogram or enema may be helpful in identifying a specific site of mechanical SBO; these studies usually show dilated loops of small intestine without localized obstruction in patients with steroid withdrawal.

Several authors have reported that serum cortisol levels are not useful in confirming the diagnosis of acute steroid

higher doses, however, did not reduce motility. These data suggest that cortisol may not influence control of gastrointestinal motor activity as an effector substance.[24] On the other hand, clinical evidence from the present study suggests that corticosteroids are important permissive hormones for normal gastrointestinal motor function and that hypoadrenalism and corticosteroid deficiency may cause suppression of gastrointestinal motility.

This study was supported in part by a grant from the Deutsche Forschungsgemeinschaft, Federal Republic of Germany (Dr Stelzner).

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[redacted]

Table 1.—Classification of Severity of Pancreatitis According to Criteria of Ranson et al[18] or McMahon et al[19]*

Ranson

On admission
  Age, >55 y
  Blood glucose, >11 mmol/L
  Leukocyte count, $>16 \times 10^9$/L
  LDH, >60 U/L
  AST, >108 U/L
During first 48 h
  Fall in hematocrit, >10%
  Serum calcium, <2.0 mmol/L
  Base deficit, >4.0 mmol/L
  Serum creatinine, >175 µmol/L
  Fluid sequestration, >6 L
  Pa_{O_2}, <7.5 kPa

McMahon

Presence of brown, free peritoneal fluid
>10 mL of free peritoneal fluid, irrespective of color
Lavage return fluid slightly brown

*LDH indicates lactate dehydrogenase; AST, aspartate aminotransferase; and Pa_{O_2}, arterial oxygen tension. Fluid sequestration was estimated by subtracting insensible perspiration and measured urinary and nasogastric

Table 2.—Basis for Classification and Clinical Characteristics in 37 Patients With Acute Pancreatitis*

	Moderate and Severe (n=18)	**Mild (n=19)**
Basis for classification		
Ranson's signs, three or more at 48 h	17	0
McMahon's signs positive	8	0
Hemorrhagic peritoneal fluid	4	0
Assisted ventilation, >5 d	7	0
Renal failure	5	0
Hepatic failure	10	3
Stress ulcer bleeding	3	0
Hypovolemic shock	3	0
Sepsis	4	0
Complications		
Death	4	0
Abscess	3	0
Pseudocyst	5	1

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This study was supported by grants from the Swedish Medical Research

We wish to thank Birgitta Norder-Hansson for technical assistance and

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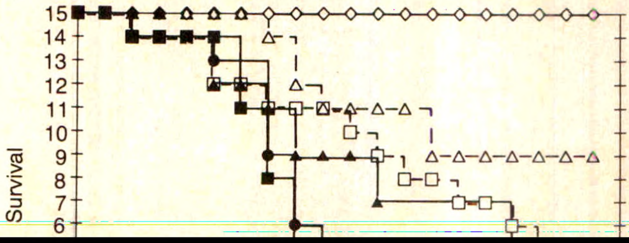
The Effect of Interleukin 1α on Survival in a Murine Model of Burn Wound Sepsis

Geoffrey M. Silver, MD; Richard L. Gamelli, MD; Michael O'Reilly, MS; James C. Hebert, MD

[redacted]

Weights and Survival of Mice Treated With IL-1α at Day 7*

Group	Average Weight, g†	Survival, Alive/Total
Sham	24.8 ± 1.44	10/10
Burn	19.9 ± 2.54	8/10
Burn + 1 ng	20.4 ± 1.60	8/10
Burn + 10 ng	21.5 ± 1.09	10/10



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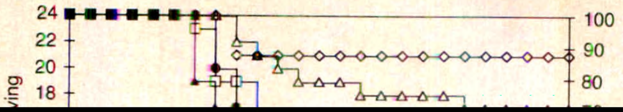

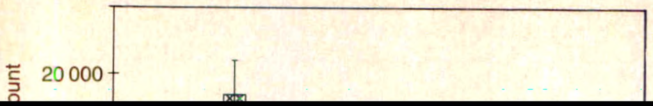

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poiesis following thermal injury and prolong survival.[23] We report here our results obtained with IL-1α, which in addition to being a hematopoietic regulator, has a number of effects on the host response to injury and infection.

We examined the ability of IL-1α to improve survival in a murine model of thermal injury with and without a superimposed bacterial burn wound inoculation. Interleukin 1α was administered either as a single dose or as twice daily injections for 7 days. In animals that received a single dose of IL-1α without a subsequent bacterial challenge, the survival was not significantly different from that of sham-burned animals. Furthermore, there was no evidence of toxicity. In fact, thermally injured animals that received higher doses of IL-1α had less weight loss than thermally injured animals that did not receive IL-1α.

[redacted]

enhance the proliferation and functional capacity of neutrophils and macrophages.

In the murine model of burn wound sepsis employed in this study, the addition of IL-1α improved survival. This survival advantage was associated with fewer positive blood cultures and an increase in the number of circulating leukocytes. The precise mechanism by which IL-1α confers improved survival has not been delineated by these studies. Interleukin 1α is considered a central mediator of the host response to injury and infection and has many effects on several cell types, organs, and organ systems. It is likely that the ability of IL-1α to improve survival is multifactorial, and further studies are required to determine its potential use in the management of infectious complications following injury.

This study was supported in part by the Mary Anne Miller Burn Fund.

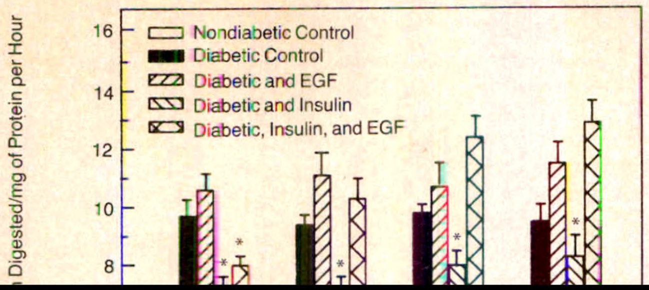
[redacted]

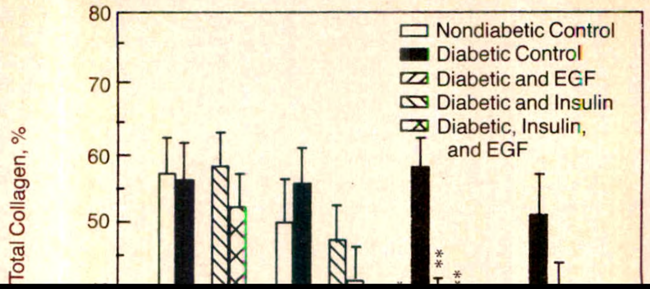
590 nm on a microtiter-plate spectrophotometer (Titertek Multiscan, Flow Laboratories, Sydney, Australia) by using the method described by Nethery et al.[7] Metalloenzyme, ie, collagenase, activity was isolated from other proteolytic activities by the addition of 20-mmol/L edetic acid (EDTA) to the above assay. The total com-

Collagenase and Protease Activity

Diabetic rats had significantly higher collagenase and protease activities than nondiabetic controls on all days studied ($P<.001$) (Figs 2 and 3). There was no significant difference in

[redacted]


n Digested/mg of Protein per Hour
16
14
12
10
8
Nondiabetic Control
Diabetic Control
Diabetic and EGF
Diabetic and Insulin
Diabetic, Insulin, and EGF
*
*
*
*
*


Total Collagen, %
80
70
60
50
Nondiabetic Control
Diabetic Control
Diabetic and EGF
Diabetic and Insulin
Diabetic, Insulin, and EGF
**
**

[redacted]

data demonstrate that a single topical application of insulin leads to normalized collagenase activity, somewhat normalized protease activity, and a decrease in the type III/total collagen ratio to near-normal levels. All of these changes, as well as the observed increase in collagen accumulation, might be associated with the temporary inhibition of proteolytic activity directed primarily at type I collagen. Current studies within this laboratory are directed toward elucidating the mechanism of the observed insulin effect.

The topical application of EGF and insulin simultaneously led to the largest and most stabile increase in wound collagen accumulation in diabetic rats. At the end of 15 days of healing, only the animals treated with the combination of insulin and EGF were continuing to acquire collagen within the granulation tissue. Collagenase activity and the type III/total collagen ratio were normalized at 15 days. The protease activity within this group was substantially increased by the 15th day of the study, and may or may not have eventually led to a decline in the amount of collagen within the wound. Currently, studies are being performed to evaluate the long-term, ie, greater than 1 month, effects of insulin, EGF, and their combination on wound healing in diabetic and nondiabetic rats.

Our data indicate that the combination of insulin and EGF act synergistically to improve several wound-healing characteristics in diabetic rats. We are modifying the analyses that we perform on the granulation tissue to employ new techniques of measuring procollagens, their messenger RNAs, and collagenase and protease inhibitors, as well as to measure directly the rate of collagen synthesis. These studies indicate the complexity of collagen metabolism during normal and pathologic wound healing, and they demonstrate the need for studies designed to evaluate "mechanisms of action" rather than "descriptive results" of growth factor use.

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[redacted]

solutions was randomly selected and administered into the left atrium during a 3-minute period in an amount equal to 5% of the animal's blood volume, as calculated from body weight.

Three treatment solutions were evaluated: Ringer's lactate, 5% serum albumin (Cutter Laboratories, West Haven, Conn), and a large fraction of HES macromolecule (HES Pz). The osmotic pressure of each solution was between 290 and 330 mOsm. The molecules that compose Ringer's lactate are each less than 100 d. Albumin, 5%,

100 g of dry weight) – ("infarcted" myocardial potassium/100 g of dry weight).

The other pair of myocardial specimens was placed in 4% formaldehyde for histologic evaluation and correlation of "infarct" size. Comparisons of microscopic changes in the infarct areas were made by pathologists who were not aware of the fluid treatments received by animals. Microscopic evaluations were made of the infarct areas with the use of four criteria: (1) coagulation necrosis, (2) polymorphonuclear infiltration, (3) hemorrhage, and (4) interstitial edema.[19,20] Each

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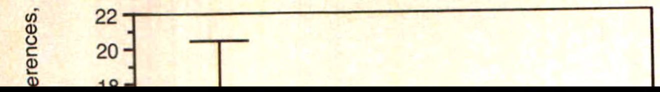

age was demonstrated almost 2 decades ago for histamine, serotonin, and bradykinin by electron microscopic studies, which were confirmed in vivo.[24,25] The endothelial cells in the

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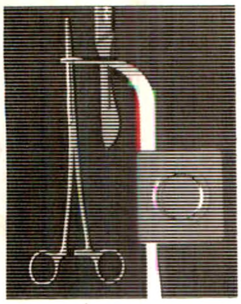

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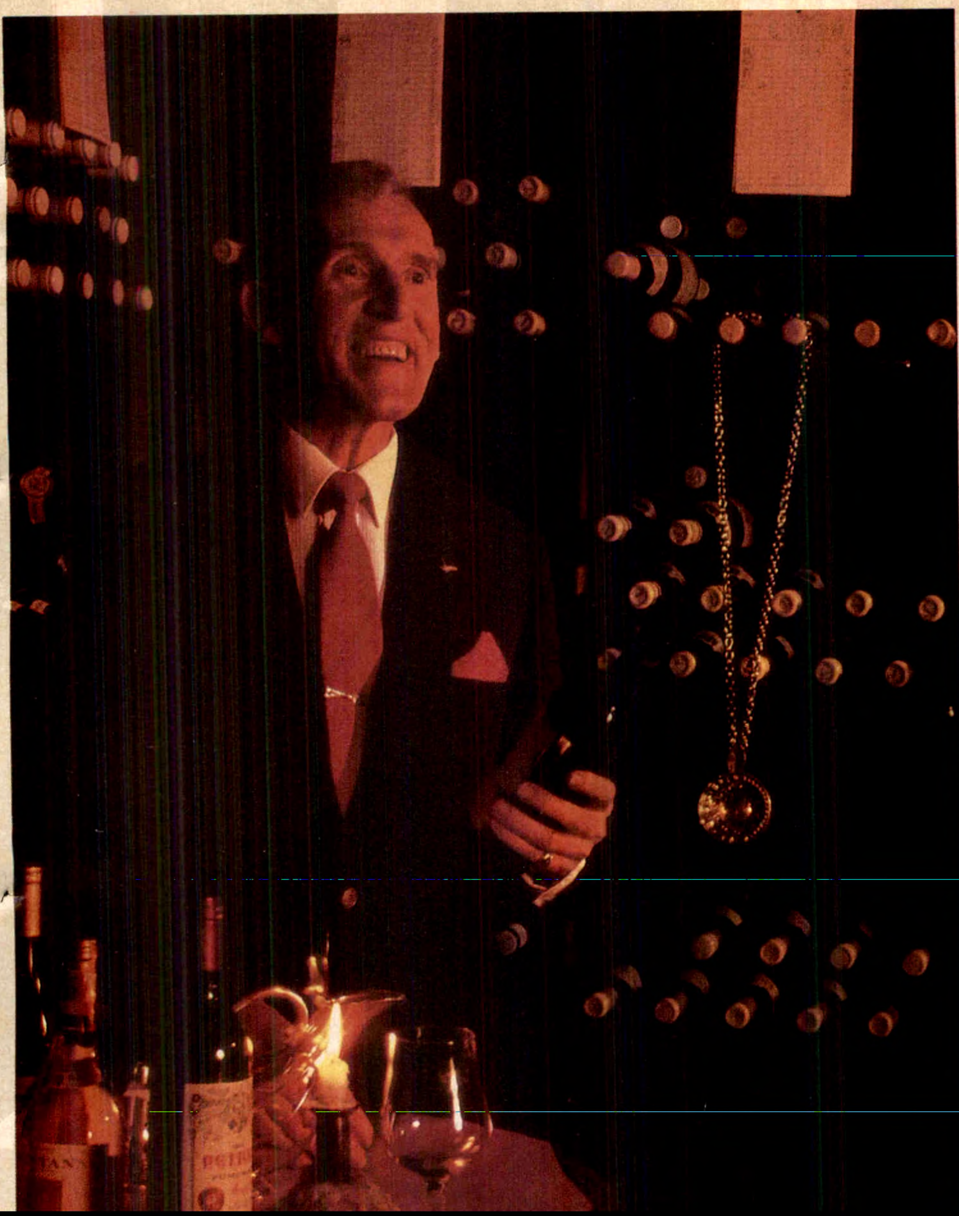

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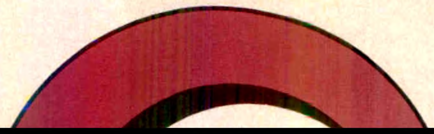

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Flatulence	<1	2
Dyspepsia	<1	1
Hematological		
Leukopenia		
<2000/mm3	<1	1

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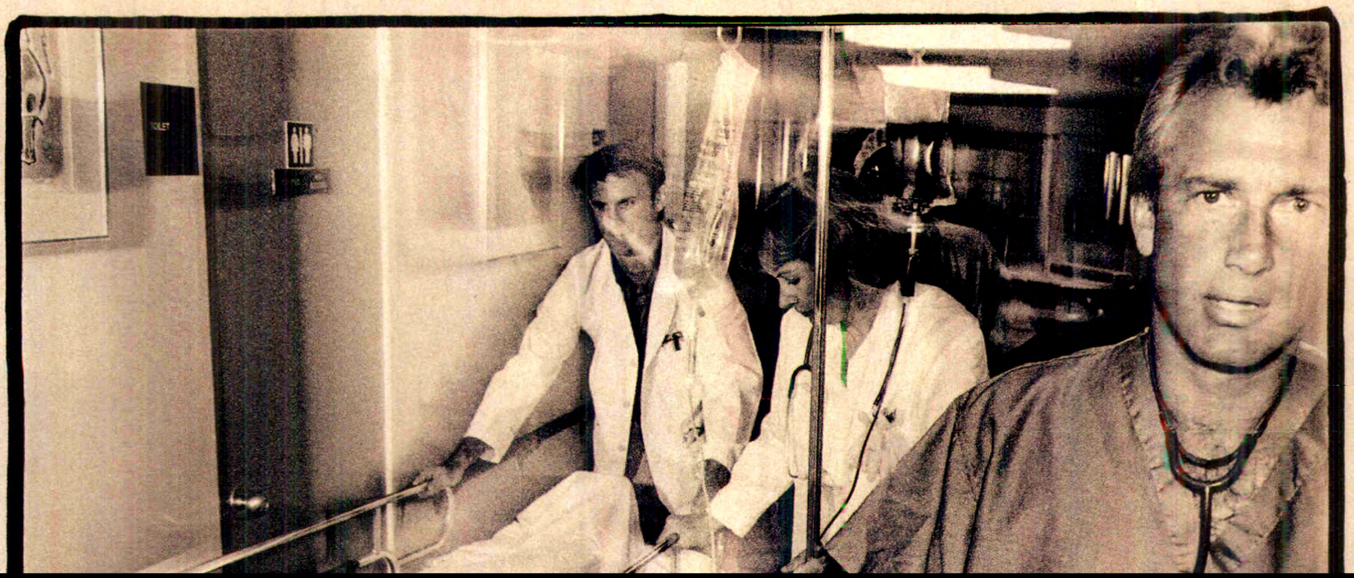

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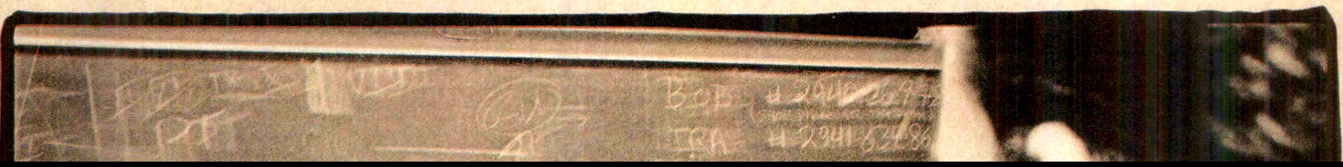

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Table 1.—The Relationship of Clinical Presentation to the Histologic Type of Duodenal Villous Tumors

Table 2.—Operative Procedures Employed for Each Histologic Subtype of Duodenal Villous Tumors

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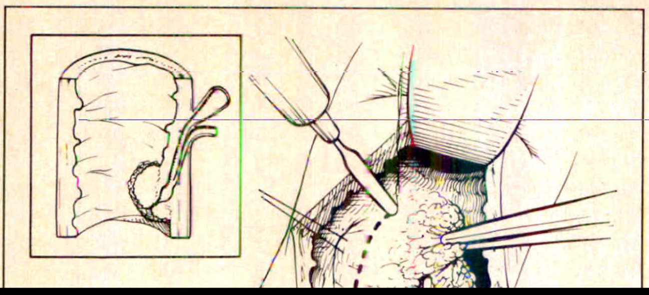

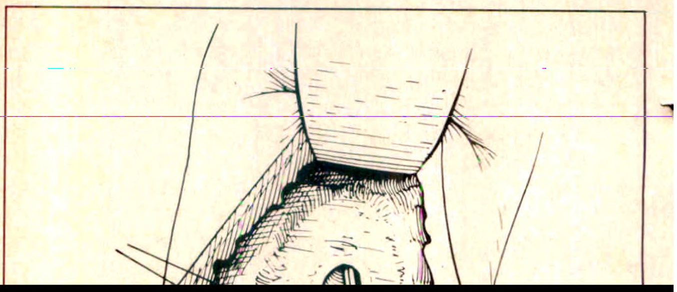

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a preexisting syndrome correlated to biliary tract disease?

WILLIAM E. STRODEL, MD, Lexington, Ky: How did the authors define gastritis? If their definition was based on endoscopic evidence alone, a problem exists in that there was actually a study done of "normal" prisoners who underwent endoscopic examinations, a sig-

[redacted]

DR HINDER: In answer to Dr Jordan's question, all patients who had a pyloroplasty also had a vagotomy. As there were only six patients with vagotomy and pyloroplasty, they would not have had a significant influence on the whole study. The patients were indeed a little older than the controls, but their mean age was about 50 years,

ing system, a stage I tumor is confined to the gastrointestinal tract, a stage II tumor extends to regional lymph nodes, a stage III tumor exhibits disease above and below the diaphragm, and a stage IV tumor exhibits widespread dissemination. Staging was done on the basis of findings of physical examination, laparotomy, bone marrow biopsies, roentgenograms, and computed tomographic scans. No general treatment policy existed for the planning and institution of therapy for gastrointestinal tract lymphomas. The extent of surgical resection and the choice of chemotherapy and radiation therapy

Table 1.—Site of Primary Gastrointestinal Lymphoma

	Stomach	**Small Bowel**	**Colon**
No. of patients	25	9	8
Mean age, y (range)	62 (22-87)	49 (17-80)	48 (30-94)
Sex, M/F	15/10	3/6	5/3
Stages I and II,			

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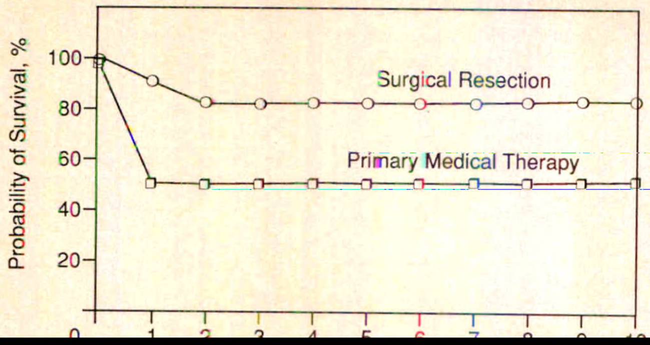
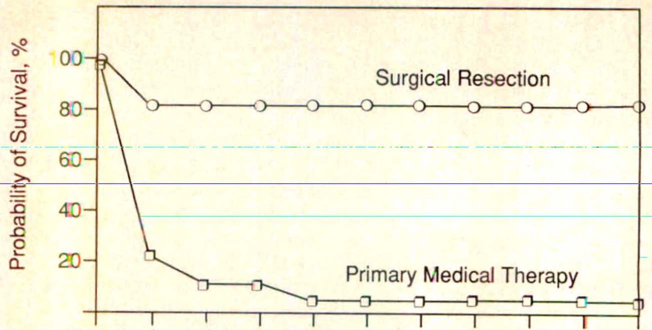

Probability of Survival, %
100
80
60
40
20
Surgical Resection
Primary Medical Therapy


Probability of Survival, %
100
80
60
40
20
Surgical Resection
Primary Medical Therapy

[redacted]

site. Gastric lymphoma occasionally perforates, and this was

[redacted]

tumor should be weighed against the potential surgical complications when primary treatment is planned.

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series underwent bilateral adrenalectomy. We advocate this approach due to the inevitable development of bilateral pheochromocytomas in this subset of pediatric patients with pheochromocytomas.[15]

resection, and the biologic behavior of the tumor. After tumor resection, we recommend lifelong follow-up of urinary catecholamine levels as a screening test for recurrence. Suspicious results should be followed up with CT and MIBG scans

[redacted]

Unilateral Neck Exploration for Primary Hyperparathyroidism

Robert J. Lucas, MD; Robert J. Welsh, MD; John L. Glover, MD

• The operative approach to primary hyperparathyroidism due to a single adenoma remains controversial. We evaluated our experience with 75 patients presenting with primary hyperparathyroidism between January 1979 and September 1988. Prior to 1985 all patients underwent bilateral exploration. During this period, ultrasonographic localization in 6 patients proved highly accurate. Subsequently, routine preoperative ultrasonographic localization was used and patients were prospectively evaluated for the following: (1) incidence of unilateral exploration, (2) accuracy of ultrasonographic localization, (3) incidence of complications, and (4) operative time. Localization permitted unilateral exploration in 19 of 36 patients, although its accuracy depended on the interest of the radiologist involved. Institution A had an accuracy of 92%, while institution B had an accuracy of only 43%. There were fewer complications with unilateral exploration, and operative time was significantly less. Unilateral exploration based on preoperative ultrasonographic localization is recommended as the initial approach to primary hyperparathyroidism due to a single adenoma.

(*Arch Surg.* 1990;125:982-985)

The objective of the surgical treatment of primary hyperparathyroidism due to a single adenoma is the removal of abnormal parathyroid tissue and the establishment of normocalcemia while avoiding hypocalcemia and persistent or recurrent hypercalcemia. The operative strategy to achieve this goal remains controversial. Traditionally, the preferred approach has been to perform a bilateral cervical exploration and to identify at least four glands at the time of the initial operation. This approach is advocated by a majority of surgeons as the best method to avoid persistent or recurrent hypercalcemia.[1-8] A minority of surgeons maintain that a unilateral exploration is sufficient if an abnormal gland and a normal gland are identified on the side of the initial exploration.[9-12] We present findings of a 10-year experience in the surgical management of primary hyperparathyroidism. During this period a strategy of preoperative localization using real-time, high-resolution, B-mode ultrasonography and subsequent unilateral exploration evolved.

patients had elevated preoperative calcium levels, varying between 2.59 mmol/L and 3.42 mmol/L, with a mean of 2.92 mmol/L. Most patients had elevated parathormone levels, although a normal parathormone level assay did not exclude any appropriate patients from further evaluation for hyperparathyroidism because of the possibility of false-negative assays. Patients in groups 1 and 2 were similar with respect to age, sex, serum calcium levels, and pathology at operation. Fifty patients had symptoms thought to be attributable to hypercalcemia. These included peptic ulcer disease, pancreatitis, arthritis, myalgias, hypertension, and psychiatric disorders ranging from depression to schizophrenia. Thirteen patients had a history of renal calculi. Again, there were no differences between patients in group 1 and group 2.

Localization by ultrasonography was performed at two institutions in a total of 40 patients. At one institution the studies were directly supervised and interpreted by a single radiologist, while at the other institution examinations were performed by sonographers and the films interpreted later by one of a group of several radiologists. Similar high-resolution ultrasonographic systems were used at both institutions, with imaging frequencies of 5.0 and 7.5 MHz. The diagnosis of parathyroid adenoma vs primary hyperplasia was made at the time of operation by the surgeon in concert with the surgical pathologist. The identification and biopsy of a definitively abnormal parathyroid gland plus a normal parathyroid gland made the diagnosis of parathyroid adenoma. The demonstration of multiple abnormal glands at operation was diagnosed as hyperplasia. Serum calcium levels were measured during the postoperative hospital course and at varying times in the subsequent follow-up. The length of operation was obtained from the operative records. Follow-up information was obtained from the hospital charts, referring physicians, and the patients themselves. The length of follow-up has ranged between 1 and 10 years.

RESULTS

Thirty-nine patients in group 1 underwent bilateral cervical exploration and identification of at least four glands. Thirty-five patients had a single adenoma excised and biopsy performed on one or two normal glands, while four patients had hyperplasia and underwent a 3.5-gland resection. In addition, one patient with a single adenoma underwent a total

[redacted]

indicated side, the abnormal gland was removed and the normal gland underwent biopsy. If both specimens were histologically confirmed, the procedure was terminated. Any doubt concerning the diagnosis mandated bilateral exploration.

Of the 36 patients in group 2, two did not undergo preoperative ultrasonography. One patient had undergone a prior radionuclide scan and we believed it was unnecessary to proceed with the ultrasonography, while the other patient had had a previous thyroid lobectomy and we believed that bilateral exploration would be indicated. At present we would perform preoperative ultrasonography in this patient.

Thirty-two patients were found to have a single adenoma, three to have hyperplasia, and one patient to have three enlarged glands, two of which the pathologist described as abnormal and the third as normal. This may represent a case of double adenoma. On the basis of the preoperative ultrasonographic findings, 19 patients underwent unilateral exploration with excision of a single adenoma and a biopsy of a normal gland. The remaining 17 patients underwent bilateral exploration.

while in two cases an adenoma was identified on the wrong side. This was a statistically significant difference between institutions ($P = .004$ by Fisher's Exact Test).

The operative time for each case was recorded and compared between bilateral and unilateral explorations. Patients who underwent additional procedures, including thyroid lobectomy or subtotal parathyroidectomy for hyperplasia, were excluded from this comparison. Nineteen patients undergoing unilateral exploration had a mean (± SD) operative time of 65.1 ± 12.8 minutes, with a s range between 45 and 95 minutes (median, 62 minutes). Forty-five patients who had bilateral exploration had a mean (± SD) operative time of 84.1 ± 24.7 minutes, with a range between 50 and 165 minutes (median, 81 minutes). These mean operative times were significantly different ($P = .002$ by Student's t test).

COMMENT

The controversial aspect concerning the operative management of primary hyperparathyroidism due to a single adenoma centers on the extent of the surgical exploration and the number of glands to be identified and resected. A number of

[redacted]

ry explorations to surgeons with limited experience after obtaining a positive study and saying "cut here."

I would like to emphasize that no matter which localization study or combination of studies is used, even when the results are positive, they do not rule out multiglandular disease. Often, such studies as ultrasonography or thallium-technetium scintigraphy may demonstrate a single lesion (apparent adenoma) when another gland (double adenoma) or all four glands (hyperplasia) are involved.

The authors also quoted Dr Wang as believing that double adenomas do not occur and that a unilateral exploration is often sufficient. Despite his many excellent contributions to parathyroid surgery, I believe Dr Wang is wrong about this and would say so if he were here.

unilateral exploration in those cases that are indicated.

Certainly, the clinical decision at the time of surgery is very important to identify other abnormalities. I don't think we would have missed the four-gland hyperplasia that Dr Block talked about; whether we would have missed the other two, I'm not certain.

I think all you can expect from pathologists at the time of examining the frozen section is to tell you it's a parathyroid. Our pathologists are good at that. Our pathologists are also, like some others, somewhat skeptical about the diagnosis of double parathyroid adenoma. It's hard to be from Michigan with Dr Block having worked in Detroit and Dr Thompson in Ann Arbor and question the procedures that they perform, but I think that our results up to the present in a relatively

[redacted]

Perioperative Variables and Correlation With Stroke*

Predictive Variable	No. With Postoperative CVA/Total No.	*P*
Age, y		
≤65	1/35	.96
>65	4/138	
Sex		
M	3/109	.89
F	2/64	
Surgical procedure		
General	5/87	.02
Other	0/86	
OR SBP, mm Hg		
<100 for ≤5 min	3/129	.47
<100 for >5 min	2/44	
>180 for ≤5 min	4/144	.84
>180 for >5 min	1/29	
Highest SBP in RR, mm Hg		
>200	0/5	.69
≤200	5/168	
Lowest SBP in RR, mm Hg		
≤100	3/35	.03
>100	2/138	
≤90	2/15	.01
>90	3/158	
History of multiple CVA		
Yes	2/42	.58
No	3/113	
TIA following CVA		
Yes	0/7	.69
No	5/146	
ASA class		
II or III	2/125	.1
IV	3/48	
Duration from CVA to surgery, mo		
≤1	1/15	.36
>1	4/158	
≤6	1/33	.96
>6	4/140	
Preoperative heparin sodium		

Perioperative Variables and Correlation With Stroke* (cont)

Predictive Variable	No. With Postoperative CVA/Total No.	*P*
Peripheral vascular disease		
Yes	3/49	.24
No	2/110	
Cause of past CVA		
Embolism	1/25	.87
Thrombosis, hemorrhage, unknown	4/148	
Cause of past CVA		
Thrombosis	1/28	.81
Thrombosis, hemorrhage, unknown	4/145	
Cause of past CVA		
Hemorrhage	2/22	.06
Thrombosis, hemorrhage, unknown	3/151	
History of carotid endarterectomy		
Yes	0/9	.83
No	5/162	

*CVA indicates cerebrovascular accident; OR, operating room; SBP, systolic blood pressure; RR, recovery room; TIA, transient ischemic attack; ASA, American Society for Anesthesia; CHF, congestive heart failure; and CAD, coronary artery disease.

(mean, 12.2 days) after surgery. No perioperative TIAs were identified. New strokes were confirmed by both neurologic examination and computed tomography. A new CVA mechanism was believed to be hemorrhagic in 3 patients, embolic in 1 patient, and unknown in 1 patient. Three of 5 patients with postoperative stroke were dead at 1 month, 4 at 3 months, and all 5 at 1 year. Causes of death in the 3 patients who suffered postoperative stroke and who died within 1 month included multiple organ failure, sepsis, and brain death. Stroke was believed to be a major contributing factor in each of these 3 patients. Cause of death in the 2 patients who survived initial hospitalization was unknown. At a mean follow-up of 19 months, 10 additional strokes had occurred, and 58 patients had died.

In contrast to this group of 173 patients, 7517 patients with no prior history of stroke underwent general anesthesia at our institution in 1982. There were no postoperative strokes ob-

[redacted]

($P = .1$) influence on outcome. Age, sex, diabetes, coronary

[redacted]

Most cerebral infarctions occur many hours to days followscribed six patients with embolic mechanisms, one with a thrombotic mechanism, two with stroke related to hypoten-

[redacted]

Although the total number of such patients studied was still small, surgery appears to be safe, even if performed soon

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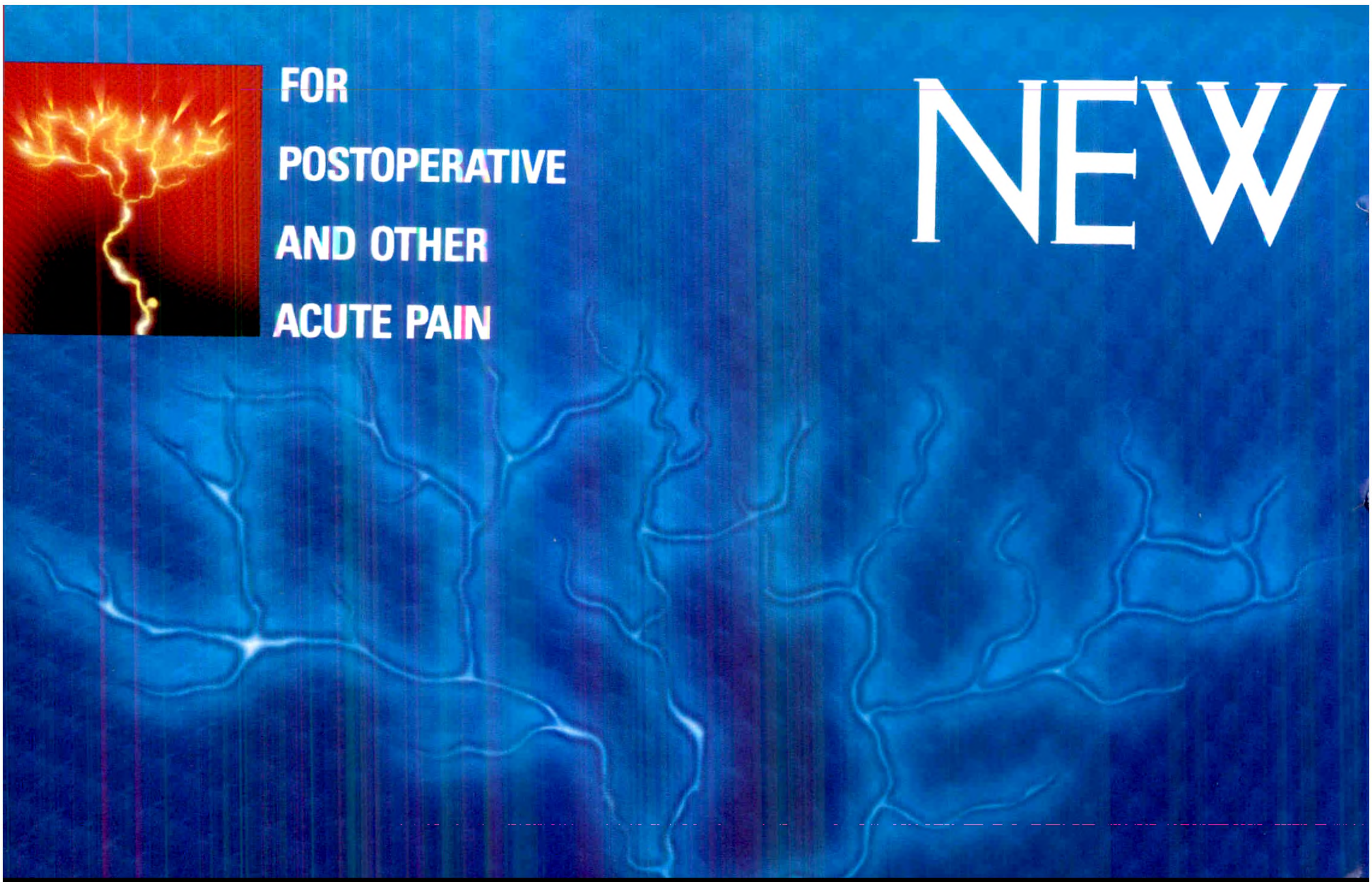

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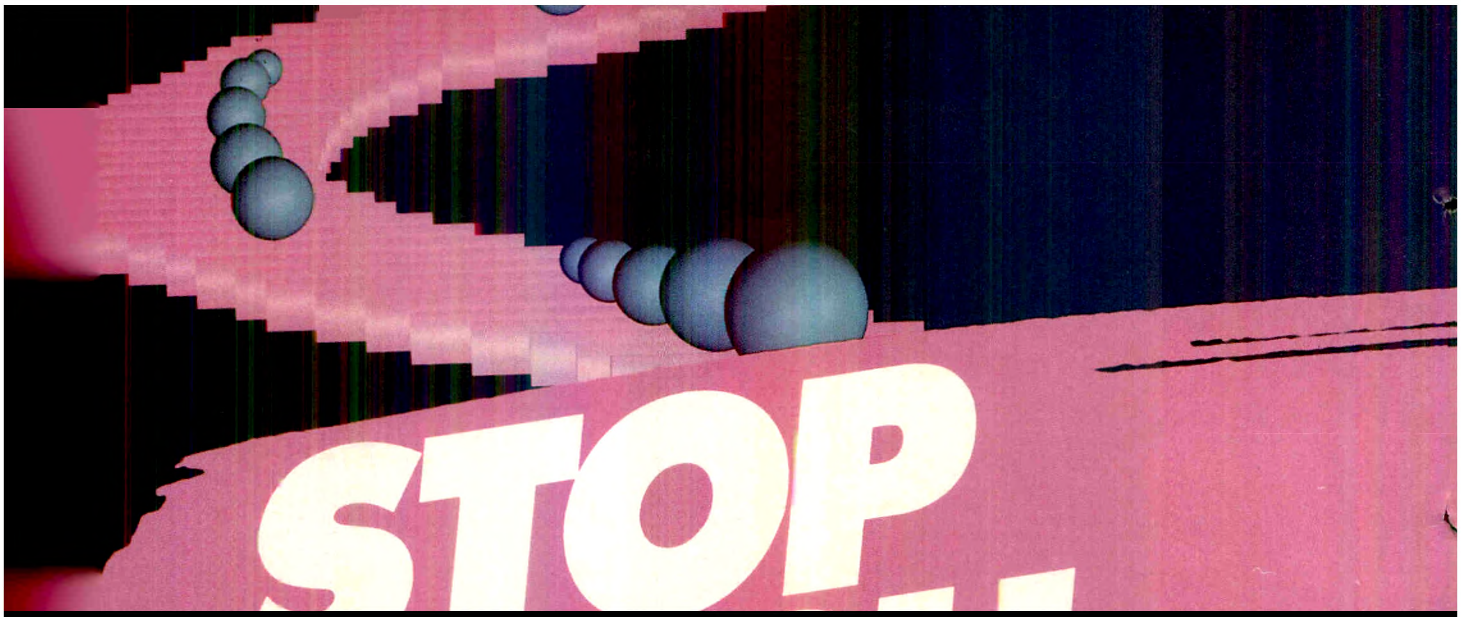

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A Comparative Study of Intraoperative Angioscopy and Completion Arteriography Following Femorodistal Bypass

B. Timothy Baxter, MD; Robert J. Rizzo, MD; William R. Flinn, MD; Carol N. Almgren;
Walter J. McCarthy, MD; William H. Pearce, MD; James S. T. Yao, MD, PhD

• A prospective comparison of the findings on standard completion arteriography with those seen using videoangioscopy was done following 49 cases of "femorodistal" bypass grafting in 47 patients. The two techniques were compared with respect to the detection of technical defects, modification of the surgical procedures, early graft patency (72 hours), and complications. Completion arteriography was specific (95%) but only moderately sensitive (67%) compared with angioscopy for detection of technical problems. Following angioscopy, significant alterations in the surgical procedure were noted in 5 (10%) of the 49 cases. Early graft failure occurred in 3 (6.1%) cases but none were identifiably due to technical problems. Four patients suffered postoperative myocardial infarctions, 2 (4.2%) of which were fatal; no patients had contrast-induced allergies or renal failure. Angioscopy was measurably more accurate for the detection of technical problems than completion arteriography, but offered little information about distal arterial anatomy that may

optic and video camera technology has allowed the production of angioscopes from 0.85 to 3.00 mm in diameter that can produce a high-resolution real-time color video image for viewing by the surgeon without compromising the sterile field. Recent reports[16,17] have suggested that this technique might replace intraoperative arteriography for detection of technical defects following femorodistal bypass grafting, but prospective studies comparing these two techniques have not previously been reported.

The present study was conducted to prospectively compare intraoperative arteriography performed routinely in our institution after completion of infrainguinal bypass procedures with angioscopic findings in the same grafts. The results of each technique were compared and analyzed with respect to the detection of technical problems, the impact on operative

[redacted]

gation of identifiable defects based on the standards developed at and reported by our institution.[1] Angioscopy was then performed in each case immediately following the completion arteriogram using fiberoptic angioscopes ranging in size from 1.4 to 2.8 mm in diameter (Olympus Corp, Lake Success, NY). The angioscope was inserted into the proximal graft through a puncture site in the case of prosthetic grafts or through side branches in the vein grafts. Warm crystalloid irrigation solution (0.9% saline solution with 2000 units of sodium heparin per liter) was infused through the cannula that had been used for the arteriogram, employing a dedicated angioscopy pump (AP-1 Angiopump, Olympus Corp). The angioscope in each case was coupled to a video camera system for display on a high-resolution color monitor for immediate assessment, and all procedures were recorded

midgraft, and distal anastomotic narrowing in 2 grafts. Angioscopy confirmed the presence of significant morphological abnormalities and accurately characterized them in 6 of these 8 cases (Table 2). Thrombus or atheromatous debris was found to be responsible for the filling defects noted on the arteriogram in 5 cases and an intimal flap caused the anastomotic stenosis seen in one other. These technical problems were corrected surgically and all six grafts remained patent postoperatively.

In two cases with abnormal completion arteriograms, angioscopy of the area in question revealed no identifiable prob-

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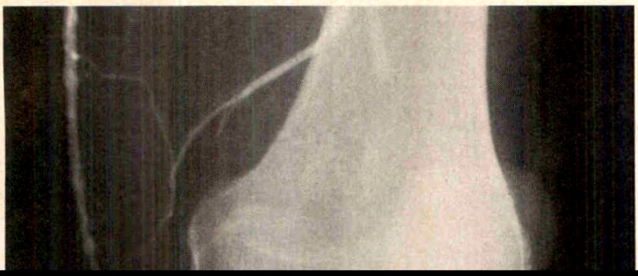

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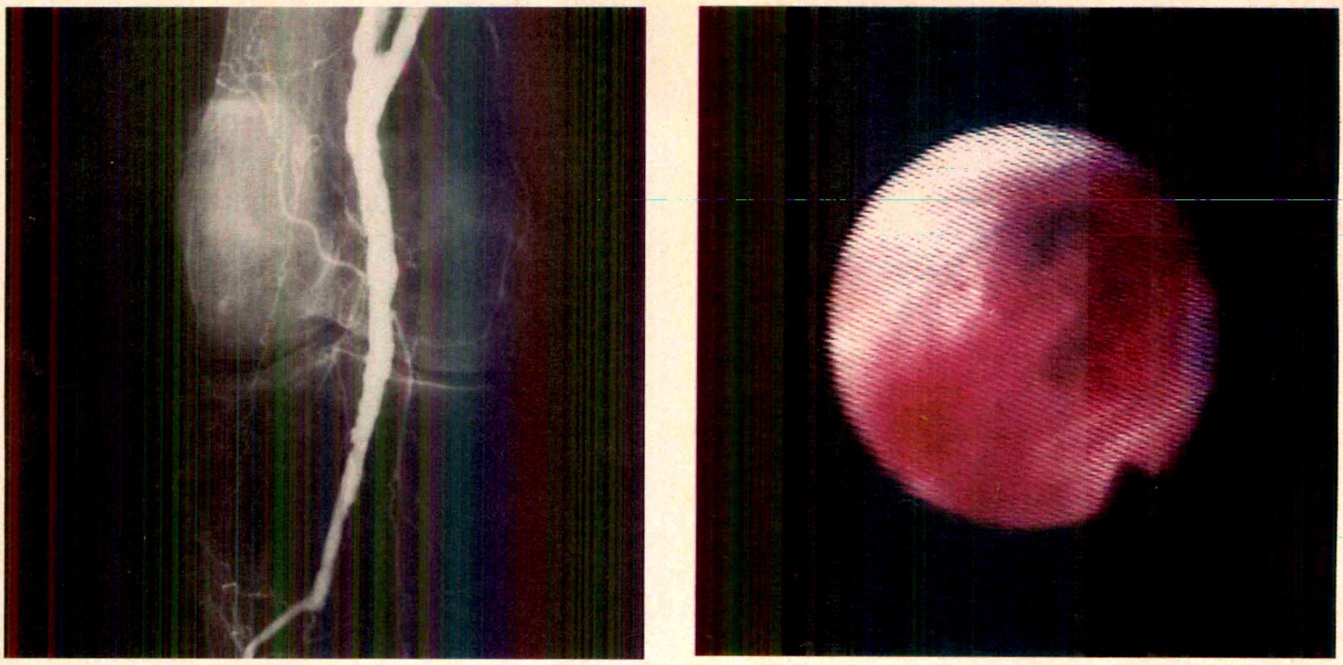

Fig 3.—Left, Following a femoropopliteal bypass with a polytetrafluoroethylene graft, the completion arteriogram was interpreted as showing no technical problems. Right, Angioscopy in this case revealed significant thrombus at and just beyond the distal anastomosis.

since adequate irrigation for maintenance of an absolutely

The accuracy of angioscopy for the detection of technical defects was superior to operative arteriography in this study. While arteriography was specific (95%), it was only moderately sensitive (67%) and these figures remain strikingly similar to those reported previously from our institution[1] in a much larger series. Experience has taught that some arteriographic findings, such as spasm in the distal vessel, do not

[redacted]

that anatomy may influence graft patency or the use of postoperative antithrombotic therapy.[22-25]

The possible hazards of angioscopy are less well defined but would include the mechanical passage of the endoscope and the irrigation fluid necessary for adequate visualization. Grundfest et al[19] described the creation of an anastomotic intimal flap by angioscopy in one case. Hashizume et al,[26] in an

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WARNING:

THE PARENTERAL USE OF COMPLEXES OF IRON AND CARBOHYDRATES HAS RESULTED IN ANAPHYLACTIC-TYPE REACTIONS. DEATHS ASSOCIATED WITH SUCH ADMINISTRATION HAVE BEEN REPORTED. THEREFORE, IMFERON SHOULD BE USED ONLY IN THOSE PATIENTS IN WHOM THE INDICATIONS HAVE BEEN CLEARLY ESTABLISHED AND LABORATORY INVESTIGATIONS CONFIRM AN IRON DEFICIENT STATE NOT AMENABLE TO ORAL IRON THERAPY.

DESCRIPTION: IMFERON (iron dextran injection, USP) is a dark brown, slightly viscous sterile liquid complex of ferric oxyhydroxide and low molecular weight dextran derivative in approximately 0.9% w/v sodium chloride for intravenous or intramuscular use. It contains the equivalent of 50 mg elemental iron (as an iron dextran complex) per mL. The pH of the solution is between 5.2 and 6.5. The multiple dose vial also contains 0.5% w/v phenol (for intramuscular use only).

INDICATIONS: Intravenous or intramuscular injections of iron dextran are indicated for treatment of patients with documented iron deficiency in whom oral administration is unsatisfactory or impossible.

CONTRAINDICATIONS: Hypersensitivity to the product. All anemias not associated with iron deficiency.

WARNINGS: See Boxed WARNING.

A risk of carcinogenesis may attend the intramuscular injection of iron-carbohydrate complexes. Such complexes have been found under experimental conditions to produce sarcoma when large doses or small doses injected repeatedly at the same site were given to rats, mice, and rabbits, and possibly in hamsters.

The long latent period between the injection of a potential carcinogen and the appearance of a tumor makes it impossible to measure accurately the risk in man. There have, however, been several reports in the literature describing tumors at the injection site in humans who had previously received intramuscular injections of iron-carbohydrate complexes.

Large intravenous doses, such as used with total dose infusions (TDI), have been associated with an increased incidence of adverse effects. The adverse effects frequently are delayed (1-2 days) reactions typified by one or more of the following symptoms: arthralgia, backache, chills, dizziness, moderate to high fever, headache, malaise, myalgia, nausea, and vomiting. The onset is usually 24-48 hours after administration and symptoms generally subside within 3-4 days (such symptoms have been well recognized since iron dextran was first used). These symptoms have also been reported following intramuscular injection and usually subside within 3-7 days. The etiology of these reactions is not known. The potential for a delayed reaction must be considered when estimating the risk/benefit of treatment.

The maximum intravenous daily dose should not exceed 2 mL undiluted iron dextran.

This preparation should be used with extreme care in patients with serious impairment of liver function.

It should not be used during the acute phase of infectious kidney disease.

Patients with rheumatoid arthritis may have an acute exacerbation of joint pain and swelling following the intravenous administration of IMFERON.

PRECAUTIONS: *General:* Unwarranted therapy with parenteral iron will cause excess storage of iron with the consequent possibility of exogenous hemosiderosis. Such iron overload is particularly apt to occur in patients with hemoglobinopathies and other refractory anemias that might be erroneously diagnosed as iron deficiency anemias.

IMFERON should be used with caution in individuals with histories of significant allergies and/or asthma.

Epinephrine should be immediately available in the event of acute hypersensitivity reactions. (Usual adult dose: 0.5 mL of a 1:1000 solution, by subcutaneous or intramuscular injection.) Note: Patients using beta-blocking agents may not respond adequately to epinephrine. Isoproterenol or similar beta-agonist agents may be required in these patients.

Reports in the literature from countries outside the United States (in particular, New Zealand) have suggested that the use of intramuscular iron dextran in neonates has been associated with an increased incidence of gram-negative sepsis, primarily due to *E. coli.* This effect from the use of IMFERON in the United States has not been reported.

Information for Patients: Patients should be advised of the potential adverse reactions associated with the use of IMFERON.

Drug/Laboratory Test Interactions: Large doses of iron dextran (5 mL or more) have been reported to give a brown color to serum from a blood sample drawn 4 hours after administration.

The drug may cause falsely elevated values of serum bilirubin and falsely decreased values of serum calcium.

Serum iron determinations by colorimetric assays may not be meaningful for 3 weeks following the administration of iron dextran, particularly after large intravenous doses.

Serum ferritin peaks approximately 7 to 9 days after an intravenous dose of IMFERON and slowly returns to normal after about 3 weeks.

Examination of the bone marrow for iron stores may not be meaningful for prolonged periods following iron dextran therapy because residual iron dextran may remain in the reticuloendothelial cells.

Prolongation of the partial thromboplastin time has been reported to occur after intravenous administration of iron dextran when the blood sample for the test is mixed with anticoagulant citrate dextrose solution, USP. This interference apparently does not occur when anticoagulant sodium citrate solution, USP is used. Blood-typing and cross-matching are not affected by iron dextran.

Bone scans involving 99mTc-diphosphonate have been reported to show a dense, crescentic area of activity in the buttocks, following the contour of the iliac crest, 1 to 6 days after intramuscular injections of IMFERON.

Bone scans with 99mTc-labeled bone seeking agents, in the presence of high serum ferritin levels or following iron dextran infusions, have been reported to show reduction of bony uptake, marked renal activity, and excessive blood pool and soft tissue accumulation.

Caution should be used in interpreting results of serum iron measurements when blood samples are obtained within 1 or 2 weeks of administration of large doses of IMFERON.

Carcinogenesis, Mutagenesis, Impairment of Fertility: See WARNINGS.

Pregnancy: Pregnancy Category C. IMFERON has been shown to be teratogenic and embryocidal in mice, rats, rabbits, dogs, and monkeys when given in doses of about 3* times the maximum human dose. No consistent adverse fetal effects were observed in mice, rats, rabbits, dogs and monkeys at doses of 50 mg iron/kg or less. Fetal and maternal toxicity has been reported in monkeys at a total intravenous dose of 90 mg iron/kg over a 14 day period. Similar effects were observed in mice and rats on administration of a single dose of 125 mg iron/kg. Fetal abnormalities in rats and dogs were observed at doses of 250 mg iron/kg and higher. The animals used in these tests were not iron deficient. There are no adequate and well-controlled studies in pregnant women. IMFERON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Placental Transfer: Various animal studies and studies in pregnant humans have demonstrated inconclusive results with respect to the placental transfer of iron dextran as iron dextran. It appears that some iron does reach the fetus, but the form in which it crosses the placenta is not clear.

Nursing Mothers: Caution should be exercised when IMFERON is administered to a nursing woman. Only traces of unmetabolized iron dextran are excreted in human milk.

Pediatric Usage: Not recommended for use in infants under 4 months of age (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: *Severe/fatal:* Anaphylactic reactions have been reported with the use of IMFERON; on rare occasions these reactions have been fatal. Such reactions, which occur most often within the first several minutes of administration, have been generally characterized by sudden onset of respiratory difficulty and/or cardiovascular collapse. The incidence of these acute hypersensitivity reactions has been estimated between 0.2% to 0.3%. (See boxed WARNING and PRECAUTIONS: *General,* pertaining to immediate availability of epinephrine.)

Mild/moderate: Delayed reactions (see WARNINGS). The incidence of delayed reactions reported in a longitudinal study of patients given multiple intravenous injections of IMFERON, usually 5 mL or greater, was approximately 8% (4% of the total number of injections given).

Other systemic/local: Isolated or multiple signs/symptoms with varying severity have been reported.

Cardiovascular: Chest pain, shock, hypotension, tachycardia, flushing. (Flushing and hypotension may occur from too rapid injections by the I.V. route.)
Dermatologic: Urticaria, pruritus, purpura, rash.
Gastrointestinal: Abdominal pain, nausea, vomiting, diarrhea.
Hematologic/lymphatic: Leucocytosis, lymphadenopathy (generally inguinal and associated with I.M. injections).

Musculoskeletal/soft tissue: Arthralgia, arthritis (may represent reactivation in patients with quiescent rheumatoid arthritis—see PRECAUTIONS: *General*), myalgia, including backache; abscess formation (sterile); necrosis; atrophy/fibrosis (I.M. injection site); cellulitis, swelling; brown skin and/or underlying tissue discoloration (staining) (See CLINICAL PHARMACOLOGY), soreness or pain at or near intramuscular injection sites, which in some isolated instances was reported to persist for over a year; variable degree of inflammation; local phlebitis at or near I.V. injection site.

Neurologic: Convulsions (may accompany anaphylaxis), syncope, headache, weakness, paresthesia, febrile episodes, chills.
Respiratory: Bronchospasm, dyspnea.
Urologic: Hematuria.
Miscellaneous: Febrile episodes, sweating, chills.

OVERDOSAGE: Overdosage with IMFERON is unlikely to be associated with any acute manifestations. Excessive doses of IMFERON beyond the requirements for restoration of hemoglobin and replenishment of iron stores, may lead to hemosiderosis. Periodic monitoring of serum ferritin levels may be helpful in recognizing a deleterious progressive accumulation of iron resulting from impaired uptake of iron from the reticuloendothelial system in concurrent medical conditions such as chronic renal failure, Hodgkins disease, and rheumatoid arthritis. The LD_{50} of IMFERON is not less than 500 mg/kg in the mouse.

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* The human dose presented here is the total iron required for treating an iron deficient state in a representative patient. The calculation represents a 50 kg patient with a hemoglobin value of 8 g/dL requiring 30 mL of IMFERON or 1500 mg iron—equivalent to 30 mg/kg.

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Reference: 1. Mangana L, Dhar SK, Smith FC, et al: Iron absorption and utilization in maintenance hemodialysis patients: Oral and intravenous routes. *Mt Sinai J Med* 1984;51:180-183.

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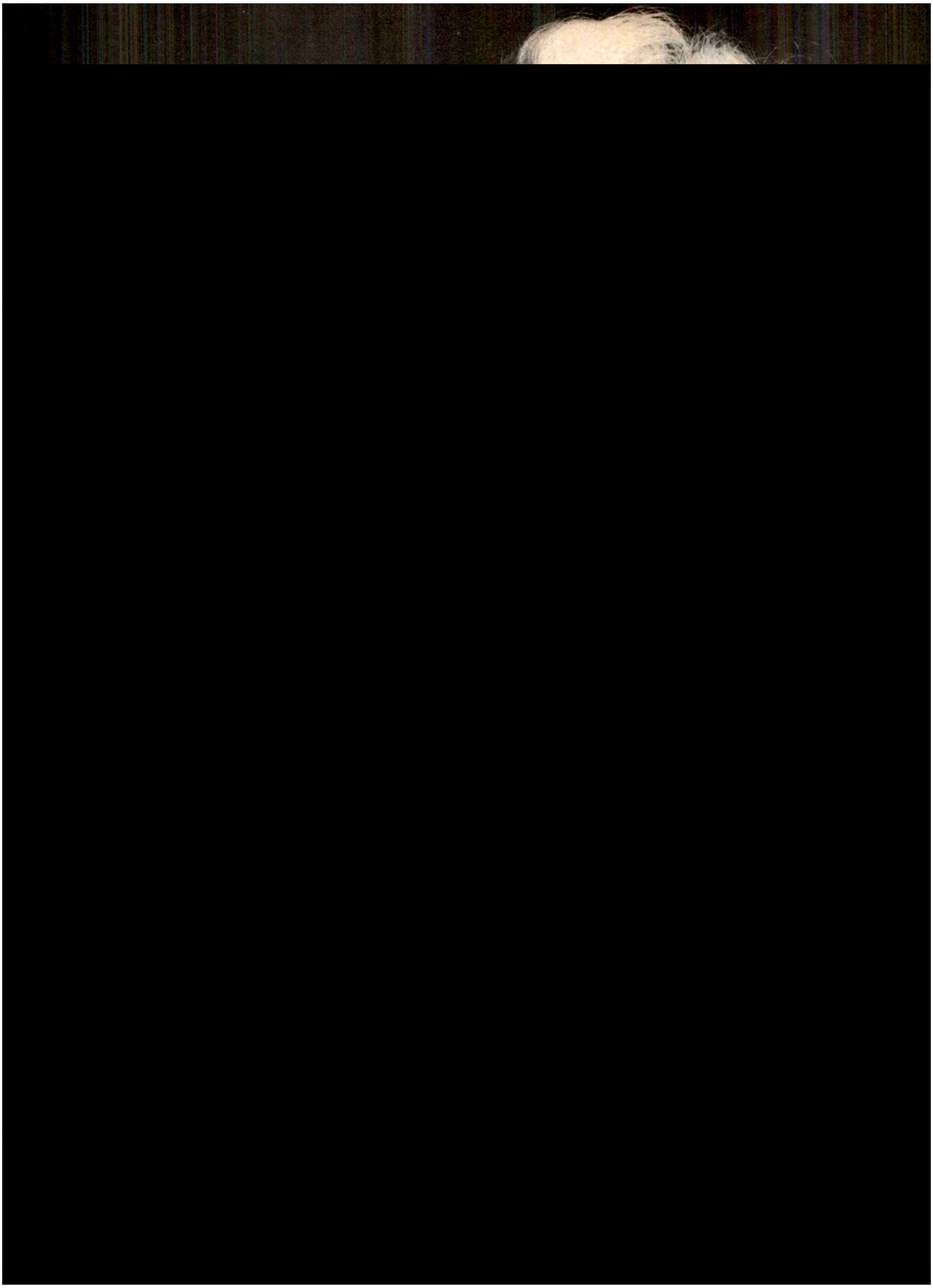

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In the management of gram-negative infection…

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experienced postoperative thrombosis due to an arterial injury from a vascular clamp. In another case, the patient had inadequate outflow that was unrecognized preoperatively, and this patient required a profundaplasty. In a third case, the patient had an antithrombin III deficiency and subsequently required long-term treatment with warfarin sodium (Coumadin).

The case of postoperative hematoma was due to excessive postoperative anticoagulation with heparin. One patient experienced a perioperative subendocardial myocardial infarction that was treated medically, and another patient developed deep venous thrombosis in the ipsilateral lower extremity 2 weeks following a laser profundaplasty. He was successfully treated with anticoagulation. One patient died 5 months postoperatively of congestive heart failure. This patient had a 60-cm LE that extended from the right external

[redacted]

“hot tip” approach delivers only thermal energy, however, and obviates the benefits of laser light–atheroma interaction.

The present study shows that direct argon ion laser radiation can be used for arterial reconstruction if it is applied in a precise fashion at low power. The LE operation does not attempt to vaporize atheromas as does the laser angioplasty procedure. Hence, much lower power is required to separate the atheroma from the media than to ablate the atheroma. The power reported for atheroma ablation ranges from 3.0 to 11.0 W,[1-3] while we required only 1.0 W for atheroma dissection and end-point welding. The power used in our study is similar to that reported by White and associates,[13,14] who welded arteries with an argon ion laser (0.5 W).

By using low power, we did not encounter perforation or thermal injury in any of the operations. The proper cleavage plane beneath the internal elastic lamina was maintained with

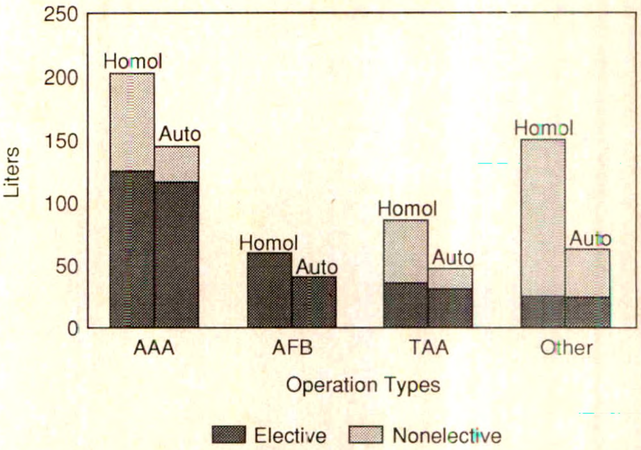
[redacted]

[redacted]

Table 1.—Distribution of Patients by Type of Operation and Urgency

Type of Operation*	No. (%)	Urgency of Operation: Elective, No. (%)	Urgency of Operation: Nonelective, No. (%)
AAA	152 (50)	131 (86)	21 (14)
AFB	64 (21)	64 (100)	0 (0)
TAA	20 (7)	12 (60)	8 (40)
Other	68 (22)	39 (57)	29 (43)
Total	**304 (100)**	**246** (81)	**58** (19)

*AAA indicates abdominal aortic aneurysmectomy; AFB, aortobilateral femoral artery bypass graft; TAA, combined thoracoabdominal aortic aneurysmectomy; and other, other types of major vascular surgical operations.



Amount of blood that was transfused. AAA indicates abdominal aortic

[redacted]

transfusion amount for the average patient was provided by

7. Peterman TA, Stoneburner RL, Allen JF, Jaffe HW, Curran JW. Risk of

[redacted]

complacent attitude about giving blood, not so much because of AIDS as because of the high incidence of non–A, non–B hepatitis. Preoperative donations, autologous transfusion, and intraoperative salvage need to be a routine part of vascular and appropriate general surgical operations. And finally, one last question: How often did you collect blood and find the amount was so small that either it was not useful or it certainly was not helpful to infuse it?

ERNEST E. MOORE, MD, Denver, Colo: Elective vascular surgery provides a uniquely favorable setting for autotransfusion; ie, there is generally predictable blood loss that enhances the efficiency of shed

activated clotting factors are discarded in the supernatant following the wash cycles.

Dr Wilson, we measure the prothrombin time, partial thromboplastin time, and values for hemoglobin, hematocrit, and platelets. Since this was not a prospective study, the data sets were not complete in all patients. Available data were subjected to analysis of variance and no important changes in these hematologic measurements were found. Diffuse intravascular coagulopathy was not observed. You will recall that 86% of these were elective operations. There is a trauma service at our institution managing most of the

[redacted]

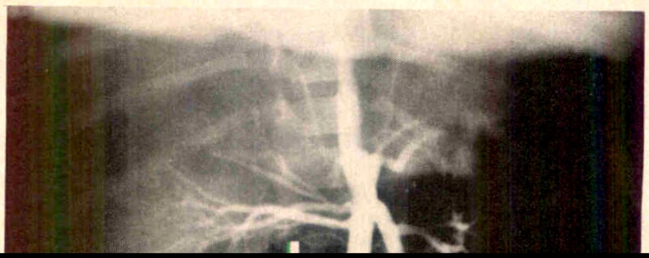
Complex Hemangiomas of Infants and Children

Individualized Management in 22 Cases

[redacted]

Clinical Characteristics of 22 Children With Complex Hemangiomas

Location of Hemangioma	No.	Age	Clinical Characteristics
Liver	7	Newborn	Congestive heart failure (n = 2), thrombocytopenia (n = 2), asymptomatic (n = 3)
Face and parotid gland	4	Newborn	Rapid enlargement (n = 3), thrombocytopenia (n = 2)



[redacted]

22 Hemangiomas

[redacted]

hemangioma. In each case, resection was curative, without morbidity. Another child presented with lower-extremity paralysis of sudden onset and was found to have hemangioma of the chest wall that extended into the spinal canal. The

[redacted]

creased risks. Further refinements in arteriographic embolization techniques, however, may make this form of therapy more desirable. Finally, several other medications have been found to be useful in the treatment of complex hemangiomas.

ROBERT J. CORRY, MD, Iowa City, Iowa: I wonder if the authors have any idea whether therapy with any of the other more specific cytokine or growth factor inhibitors, such as cyclosporine, might be more effective than prednisone therapy. Would the authors consider direct arterial infusion of some of these newer preparations?

NORMAN W. THOMPSON, MD, Ann Arbor, Mich: Could the authors

[redacted]

the host and persist. Sometimes it is hard to distinguish between the two initially, and the literature reflects this. Some of the more complex of these latter lesions, also called capillary/cavernous hemangiomas, can be associated with arteriovenous fistulas located in deeper tissue. Only then should these patients be considered candidates for embolization.

[redacted]

extent of hepatic metastases, and presence of measurable malignant disease. Patients were then randomized to treatment with intra-arterial floxuridine (FUDR) by hepatic artery infusion or systemic intravenous fluorouracil (5-FU). There was no crossover at the time of tumor progression. Standard fluorouracil therapy was given at a dose of 500 mg/m^2 by intravenous bolus for 5 consecutive days at 5-week intervals. Patients in the systemic fluorouracil arm proceeded directly to outpatient treatment, while patients in the floxuridine arm proceeded to hepatic angiography, laparotomy for pump implantation, hepatic arterial perfusion study to document adequate flow throughout the liver, and then to treatment. Floxuridine was delivered by continuous hepatic artery infusion at a dosage of 0.3 mg/kg per day for 14 days, followed by 14 days of heparinized saline. Cycles were repeated each month. This dosage administration schedule was chosen since it was the same as reported by the University of Michigan (Ann Arbor) trials.

Since this represented a multi-institution cooperative trial, surgical quality control was carefully monitored. Standard surgical technique for hepatic artery catheter placement and infusion pump implantation was performed as described by Niederhuber and Ensminger.[11] Following thorough abdominal exploration, the catheter was placed into the gastroduodenal artery so that the catheter tip lay at the junction of the hepatic artery but not projecting into it. The distal gastroduodenal and right gastric arteries were ligated to reduce the risk of floxuridine perfusion of the stomach and duodenum. Because of the reported incidence of chemical cholecystitis, cholecystectomy was performed. Patients who had a nonstandard vascular supply to the liver were treated according to the blood flow contribution of the vessels. Small arteries associated with other major vessels were treated by ligation of the nondominant vessel. Patients with a

mum-likelihood estimate statistic for treatment from a model containing treatment and the other significant covariates. When F values are given for other measures of treatment efficacy, they are based on a χ^2 statistic. All P values are two-sided.

Patients were followed up, and time to progression and overall survival was determined. No patients were unavailable for follow-up. All of the 69 study patients have died.

RESULTS

Patient characteristics according to treatment arm are given in Table 1. The two groups were well matched according to sex, age, performance score, the presence of symptomatic metastases, presence of measurable disease, percent of liver parenchyma involved by metastases, prerandomization resection of the primary tumor, and tumor grade. Performance status was graded according to ECOG scores, where 0 is fully ambulatory and 4 is totally disabled. Tumors were graded according to Broder's classification, where 1 is well differentiated and 4 is poorly differentiated. Liver involvement was graded according to whether metastatic disease replaced less than or greater than 25% of the hepatic parenchyma.

Surgical Complications

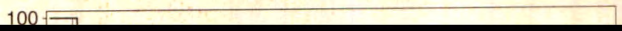
Extrahepatic Disease.—Preoperative angiography demonstrated extensive metastases with extrinsic compression of the hepatic artery, suggesting extrahepatic metastases and an anomalous arterial circulation in one patient. No surgery was performed. Arteriography demonstrated extrahepatic tient had a replaced right hepatic artery, and a catheter was placed into a polytef graft, which was sewn end-to-side into the replaced right hepatic artery arising from the superior mesenteric artery. The other patient had a normal anatomy, and the occlusion of the right hepatic artery was noted on the postoperative hepatic arterial perfusion study scan.

Nonstandard Anatomy.—Four patients (11%) were found to have nonstandard anatomies, which were noted on the preoperative angiogram and dealt with surgically. One patient had significant stenosis of the superior mesenteric artery and received a major portion of blood to the small bowel through the gastroduodenal artery. The perfusion catheter was placed directly into the hepatic artery, and a macroaggregated ^{99m}Tc-albumin scan showed a small area in the left lobe of the liver that was not well perfused, probably because of an inadequate mixing effect or streaming of the flow. Since 80%

abnormalities were frequently prolonged and required reduction in the dosage of floxuridine delivered by the pump or in delay in the chemotherapy infusion cycle. Severe, multiple, intrahepatic biliary strictures developed in one woman after 22 months of floxuridine therapy and required external biliary drainage.

Gastritis.—Despite operative measures to diminish perfusion of the stomach and duodenum, chemical gastritis developed in four patients (13%). This responded to dose reduction of floxuridine or to delay of treatment cycles. There were no instances of gastrointestinal bleeding in treated patients.

Intravenous Fluorouracil.—The major side effects of intensive-course fluorouracil were as anticipated and consisted of reversible stomatitis, diarrhea, and leukopenia. These toxic reactions were considered severe in 30%, 18%, and 45% of patients, respectively. There were no episodes of life-threat-



[redacted]

was the dominant site of disease, and they did have pumps implanted and did receive intrahepatic floxuridine. We thought that to exclude this group would represent selection of a more favorable group since the incidence of extrahepatic disease in the systemic therapy group was unknown, and presumably clinical staging was equally inaccurate in both groups. We did compare the 7 patients found at laparotomy to have extrahepatic disease who had infusion pumps implanted with the 24 patients receiving pumps who had no evidence of extrahepatic disease. Those with extrahepatic disease had

[redacted]

cycles for patients who had not experienced tumor progression. The actual dose administered per cycle for patients continuing on the study decreased substantially and was less than 50% of the starting dose by the fourth treatment cycle. Some elevation of liver enzyme levels is almost universally seen in patients treated with intra-arterial floxuridine (79% to 96%).[23,25] Although our starting dose of floxuridine (0.3 mg/kg per day) may have been higher than optimal based on the observed toxic reactions, dosage reduction of floxuridine to 0.2 mg/kg per day has been only partially effective in limiting

Iatrogenic Injury to the Bile Duct

Who, How, Where?

[redacted]

The Bismuth grades and final outcome of the 81 bile duct strictures are shown in Table 1. All 32 patients with type 1 (low) strictures had undergone common bile duct exploration at the time of cholecystectomy, compared with only 3 of the 49 with types 2 through 4 (high) strictures. Of the 32 low strictures, 20 were referred without further operative interference, but 12 had already had one or two previous attempts at repair. Three patients had a successful end-to-end anastomosis at the time of the injury. Four patients with strictures (one recurrent) at the termination of the common bile duct were treated by transduodenal sphincteroplasty. The other 25,

Table 1.—Grades[11] and Outcomes in 48 New and 33 Recurrent Iatrogenic Bile Duct Strictures

Type	No.	Recurrent Stricture, No. (%)	Mortality, No. (%)	Chronic Morbidity, No.
1	33	12 (36)	0	0
2	28	8 (28)	2 (7)	3
3	11	5 (66)	6 (54)	3
4	9	8 (90)	7 (77)	2

[redacted]

Bile duct injuries occurred at all types of institutions, and the percentages observed in our series (21% university hospital, 26% affiliated hospital, 51% community hospital) probably reflect the relative numbers of biliary operations carried out at these different types of hospitals. Some earlier series suggested that inexperience was an important cause of operative errors.[14,22] The difficulty of an operation cannot always be anticipated, and cholecystectomy should not be delegated to an unsupervised junior surgeon. However, duct injury is not the prerogative of the inexperienced.[23,24] A trained surgeon operated on 64% of our patients and assisted in a further 10%. Andren-Sandberg et al[5] noted that 80% of surgeons who

5. Andren-Sandberg A, Alinder G, Bengmark S. Accidental lesions of the common bile duct at cholecystectomy. *Ann Surg*. 1985;201:328-332.

6. Henry ML, Carey LC. Complications of cholecystectomy. *Surg Clin North Am*. 1983;63:1191-1204.

7. Johnson GW. Iatrogenic bile duct stricture: an avoidable surgical hazard? *Br J Surg*. 1986;73:245-246.

8. Collins PG, Gorey TF. Iatrogenic biliary stricture: presentation and management. *Br J Surg*. 1984;71:980-982.

9. Aranka GV, Sonta SJ, Greenlee HC. Cholecystectomy in cirrhotic patients: a formidable operation. *Am J Surg*. 1982;143:55-60

10. Goor DA, Ebert PA. Anomalies of the biliary tree. *Arch Surg*. 1972;104:302-309.

11. Bismuth H. Postoperative strictures of the biliary tract. In: Blumgart LH, ed. *The Biliary Tract*. New York, NY: Churchill-Livingstone Inc; 1982;209-218.

[redacted]

reading for the plaintiff's bar. I hasten to attempt to defuse this ticking bomb.

In the article, Dr Moossa and his coauthors deprecate the early dissection of Calot's triangle in favor of beginning the dissection at the fundus. I disagree. I routinely dissect the triangle at the start of the operation, identify the cystic artery, and divide it after visualizing the arborization of the artery on the gallbladder. The cystic duct is then

tained injury to the extrahepatic biliary system during cholecystectomy were referred to the authors over an 18-year period. The most surprising finding was that more than one third of the strictures were located in the distal bile duct. All distal strictures followed common bile duct exploration, and the authors theorize that the strictures occurred because of forceful instrumentation or dilation of the distal duct. Such distal strictures have been rare in our experience and in

[redacted]

Pancreatitis After Endoscopic Retrograde Cholangiopancreatography

[redacted]

Repeated injections into the pancreatic duct were documented in nine patients during attempts to visualize the common bile duct. Six patients underwent attempted endoscopic sphincterotomy, and one patient underwent biliary manometry. Antibiotics were employed prophylactically in only four patients in this entire series.

The pancreatic ductal system was visualized in 20 patients. Fifteen of these systems contained no abnormalities, while 4 were seen to contain some degree of ductal dilatation. A single case of pancreas divisum was noted. No pseudocysts or ductal injuries were documented. Of the 4 patients with suspected

The six patients with SP after ERCP all required monitoring and treatment in the intensive care unit. Their average length of hospitalization was 20 days, and five of the six required TPN. Five of these six patients also required surgical treatment during their short-term hospitalization, and three patients ultimately died of complications of their disease. Two patients had documented repeated injections into the pancreatic duct, and no patient underwent attempted sphincterotomy or manometric studies. The APACHE (*a*cute *p*hysiology *a*nd chronic *h*ealth evaluation) II score calculated in two of the lethal cases was 35 and 32,

[redacted]

review. This is somewhat at variance with data in the literature regarding the severity of the resulting pancreatitis. Although Ruppin et al[7] reported a series of ERCP complica-

[redacted]

similar to those in other cases of complicated acute pancreatitis and should be the following: (1) documentation of infection by culture or Gram's stain after percutaneous aspiration of

Discussion

A. RAHIM MOOSSA, MD, San Diego, Calif: During the past 6 years, we have seen 11 such cases in which a disaster of some sort occurred during or after ERCP, and we have had 2 deaths, 1 from fulminant pancreatitis as described herein. The tragedy of that case was that the patient had a normal pancreas, and the indication for ERCP was, at best, debatable. The second patient died of *Pseudomonas* sepsis following forceful injection of dye through an obstructed papilla of Vater.

[redacted]

have only uncovered the tip of the iceberg. The frequency and seriousness of post-ERCP pancreatitis has long gone unnoticed for several reasons. First, endoscopists are not recording these complications. When I approached gastroenterologists about the details of a particular case, I asked if they had had any other cases; they would say, "Yes, well, there were one or two other patients we had last year, but I cannot remember their names and have no way of retrieving the names." Clearly, some endoscopists are not recording and reporting

[redacted]

[redacted]

namic data derived from PAC. As a result, in their study 60% of physicians made a major alteration in therapy. Fein et al[5] demonstrated that the clinical diagnosis of pulmonary edema in a medical ICU population was often inaccurate and PAC was needed to make correct diagnosis and to optimize therapy. Finally, Eisenberg et al,[4] in a medical ICU/CCU population, showed that clinical hemodynamic variables were accurately predicted by physicians only 50% of the time. Pulmonary artery wedge pressure was correctly predicted in only 30% of patients; both overestimation and underestimation of PAWP occurred, and overestimation of CO predominated. Furthermore, in their study treatment was altered after PAC in greater than 50% of the population and an entirely new therapeutic modality was instituted in nearly one third of patients.

[redacted]

prompted an alteration in therapy in 50% of the patients. Major therapy changes were much more frequent in patients with inaccurate predictions of PAWP. Several factors may have accounted for the inaccuracy of prediction. Although surgical house staff were requested to predict hemodynamic measurements approximately 30 minutes prior to PAC insertion, it was possible that fluid therapy and/or vasopressor support prior to insertion, particularly in patients with hypotension (40.9%), may have affected predictive ability. In the surgical ICU population with a significant proportion of multiorgan failure, clinical findings and PAC data may not necessarily correlate as well as in a medical ICU or a CCU population.

The results of our study represent a broad clinical experience that may be generalized to represent similar types of

Oral Glutamine Accelerates Healing of the Small Intestine and Improves Outcome After Whole Abdominal Radiation

V. Suzanne Klimberg, MD; Rabih M. Salloum, MD; Michael Kasper, MD; Donald A. Plumley, MD;

[redacted]

water. Diets were isonitrogenous and contained 1% glucose for palatability. The animals were allowed to drink the oral diets, and intake was controlled such that each pair of rats in the glutamine and glycine groups consumed an equivalent volume of fluid per 24-hour period. In addition to ensuring that the animals were pair fed, daily weights were obtained on each rat and the frequency of bloody diarrhea was observed. The number of deaths in each group was tabulated. Autopsy was performed on all animals that died, and the intestine was carefully inspected for evidence of perforation.

Control rats were not irradiated but were otherwise treated identi-

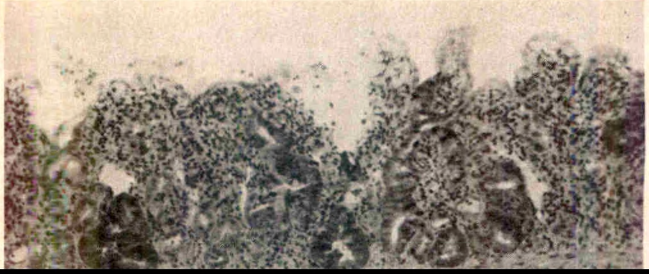
Table 1.—Morbidity and Mortality

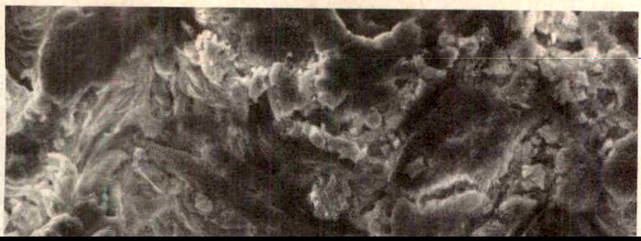
	Mean ± SEM			
Group and Treatment	Oral Intake, mL/d	Weight Loss, %	Bowel Perforation, No.	Survival, No. (%)
Group 1				
Radiation and				

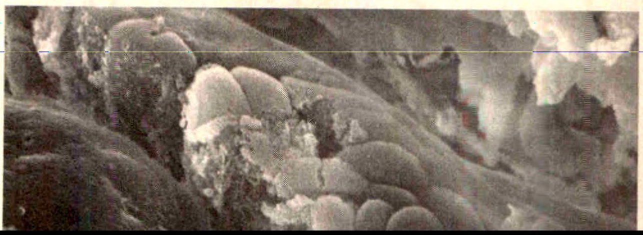
[redacted]

Group and Treatment	Mean ± SEM Bowel Length, cm	 Bowel Weight, g	 Mucosa Weight, g
Group 1			
Radiation and glutamine (n = 10)	98 ± 4	5.38 ± 0.23	0.81 ± 0.04
Radiation and [redacted]	[redacted]	[redacted]	[redacted]

Table 3.—Intestinal Morphometrics







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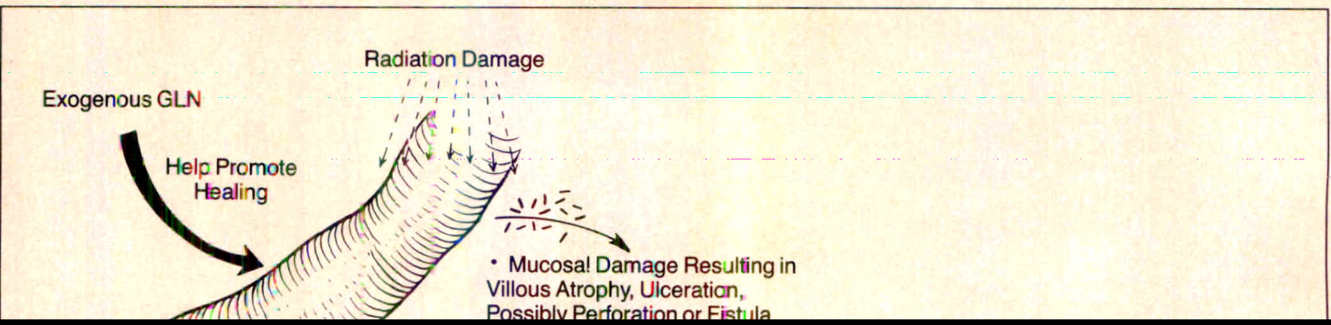

Radiation Damage
Exogenous GLN
Help Promote Healing
• Mucosal Damage Resulting in Villous Atrophy, Ulceration, Possibly Perforation or Fistula

[redacted]

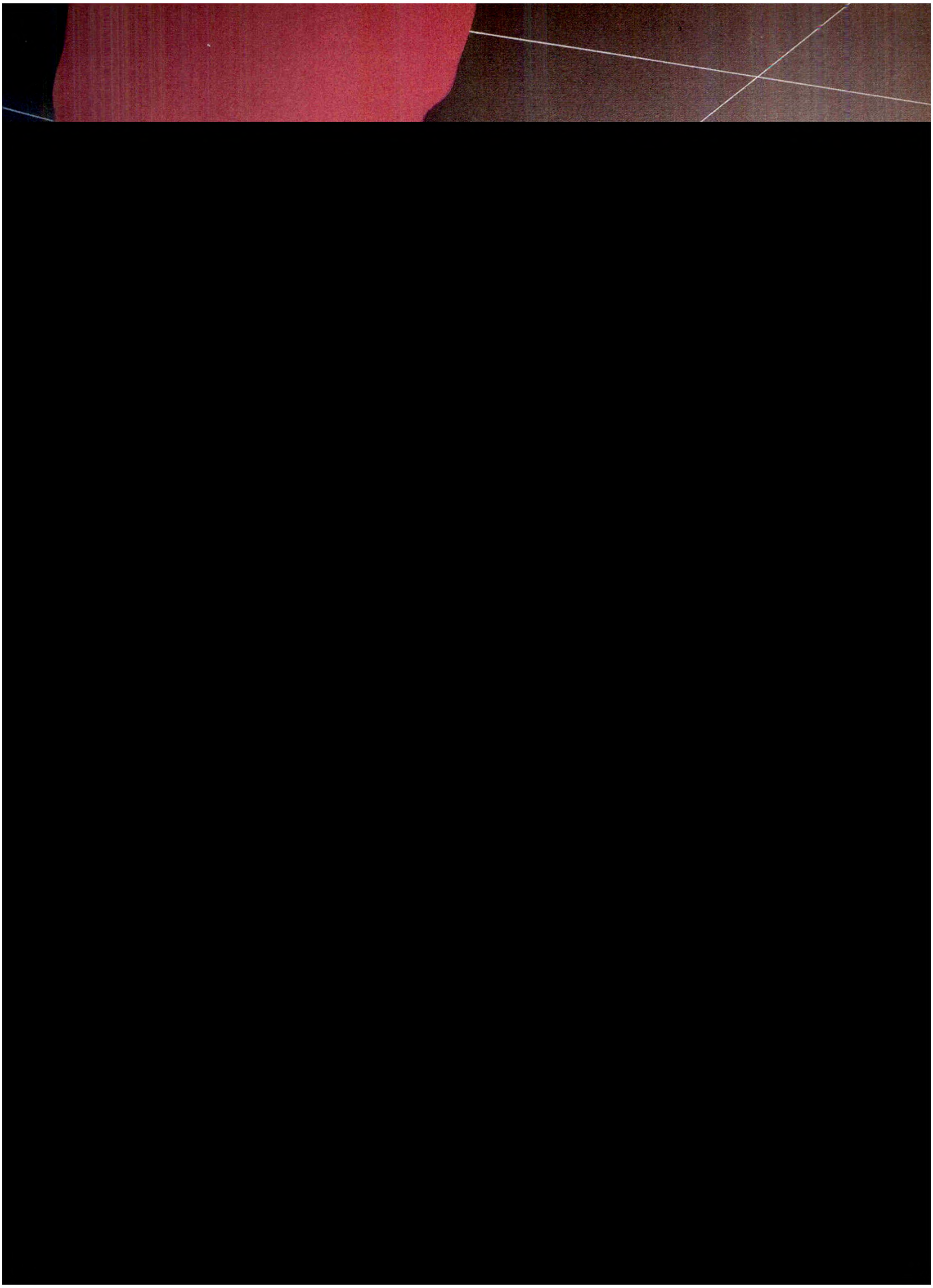
ing fluorouracil. Provision of a glutamine-enriched oral diet before abdominal irradiation affords similar mucosal protec-

[redacted]

insult, it is characterized by significant ulceration of the gut mucosa, and systemic responses occur that are associated

IT'S A WAR IN THERE

[redacted]



MEZLIN® IV/IM

mezlocillin sodium

MEZLIN®

[redacted]

Massive Screening for Colorectal Cancer

A Single Institution's Public Commitment

Nicholas J. Petrelli, MD; Michael Palmer, MD; Arthur Michalek, PhD; Lemuel Herrera, MD;
Irving Mink, MS; Gayle Bersani, RN; K. Michael Cummings, PhD

• Data from three massive screening programs for the detection of colorectal cancer and adenomatous polyps were reproducible through the collaboration of several departments at Roswell Park Memorial Institute, Buffalo, NY. The majority of

MATERIALS AND METHODS

In February 1987, a total of 48 606 stool guaiac slide kits (Hemoccult II; Smith Kline Diagnostics Inc, Philadelphia, Pa) were distributed

[redacted]

(2%). Unspecified benign conditions were noted in 47 patients (14%). Only 24 screenees (7%) were told that the cause of their

Table 1.—Diagnostic Evaluations of Screenees With Positive Results

[redacted]

been criticized for not being cost-effective. A crude measure of the cost of case detection in the 1984 program was made by dividing an estimate of the cost of screening by the number of persons with cancer identified through screening (Table 3). Since the stool occult blood kits and television time were donated, these costs were not included in the estimate of the cost of screening. Screening costs included personnel required to test and record results, follow-up of individuals with

[redacted]

Although colonoscopy on a selected group of patients with negative test results would give some idea as to the important incidence of false-negative values, this was not performed. However, the names of all screenees in all three programs were matched against the names of patients with colorectal cancer reported to the Western New York Tumor Registry as a crude assessment of the false-negative rate. The results have been previously summarized.[6,7]

patients with active

[redacted]

Zantac® Injection
(ranitidine hydrochloride)

BRIEF SUMMARY

Zantac® Injection Premixed
(ranitidine hydrochloride)

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® Injection/Zantac® Injection Premixed product labeling.
INDICATIONS AND USAGE: Zantac® Injection and Zantac® Injection Premixed are indicated in some hospitalized patients with pathological hypersecretory conditions or intractable duodenal ulcers, or as an alternative to the oral dosage form for short-term use in patients who are unable to take oral medication.
CONTRAINDICATIONS: Zantac® Injection and Zantac® Injection Premixed are contraindicated for patients known to have hypersensitivity to the drug.
PRECAUTIONS: General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.
3. In controlled studies in normal volunteers, elevations in SGPT have been observed when H_2-antagonists have been administered intravenously at greater than recommended doses for five days or longer. Therefore, it seems prudent in patients receiving intravenous (IV) ranitidine at doses greater than or equal to 100 mg qid for periods of five days or longer to monitor SGPT daily (from day 5) for the remainder of IV therapy.
4. Bradycardia in association with rapid administration of Zantac® Injection has been reported rarely, usually in patients with factors predisposing to cardiac rhythm disturbances. Recommended rates of administration should not be exceeded (see DOSAGE AND ADMINISTRATION).
Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.
Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in

Information
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[redacted]

Table 1.—Patient Demographics and Associated Risk Factors*

Table 4.—Primary Crude Patency Rates at 6 Months by Graft Material

[redacted]

Sclerosing Cholangitis Induced by Formaldehyde Solution Injected

[redacted]

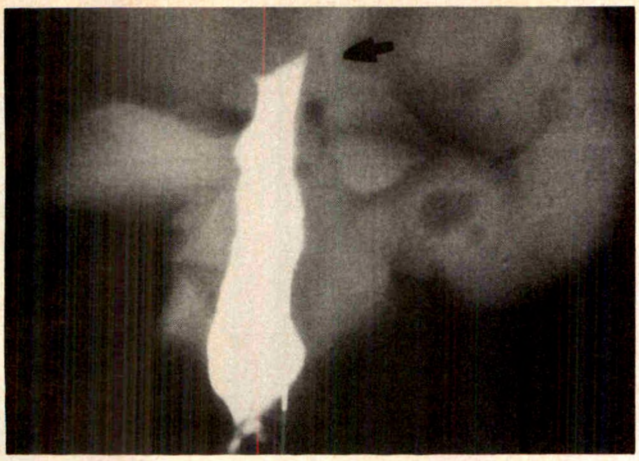


Fig 5.—Cholangiogram in a rat from group D1, 3 months after injection of 0.15 mL of 2% formaldehyde solution into the biliary tract. The arrow shows strictures at the level of the convergence and of the ampulla with marked dilatation of the biliary tree.

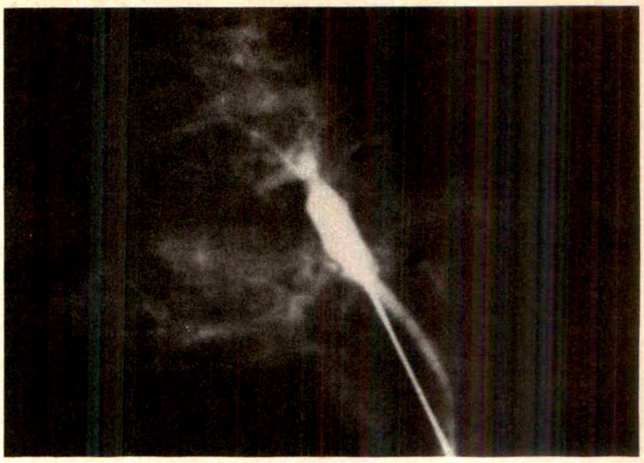
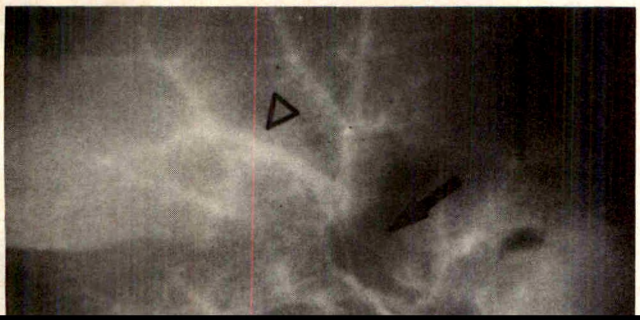


Fig 7.—Cholangiogram of a rat from group D1, 3 months after injection of 0.15 mL of 2% formaldehyde solution into the biliary tract. Note the stricture of the intrahepatic bile duct and of the convergence with dilatation between the two stenoses (arrows).



isotonic saline, hypertonic saline, and 0.5% formaldehyde solutions, we never observed periductal sclerosis or strictures on cholangiograms. The 2% formaldehyde solution, which corresponds to the concentration used to sterilize human hydatid cysts, caused sclerosing cholangitis in most of the rats and pseudocirrhosis in some of them 3 months after its injection in the biliary tree; in these rats, cholangiograms confirmed the histologic findings.

The pathogenesis of these lesions remains conjectural. The lesions might be related to an immunologic mechanism, which may explain their late development and, in some clinical

[redacted]

[redacted]

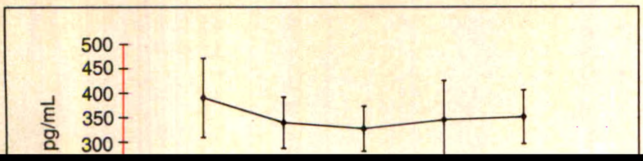
TIMENTIN® **sterile ticarcillin disodium and clavulanate potassium** for Intravenous Administration

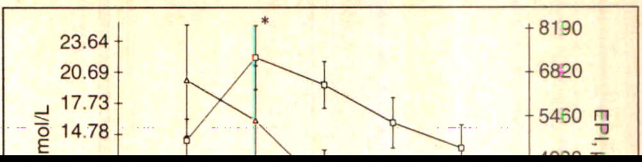
INDICATIONS AND USAGE: TIMENTIN® is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

[redacted]

Cardiovascular and Neurohumoral Responses Following Burn Injury

[redacted]


pg/mL
500
450
400
350
300


mol/L
23.64
20.69
17.73
14.78
*
8190
6820
5460
EPI,

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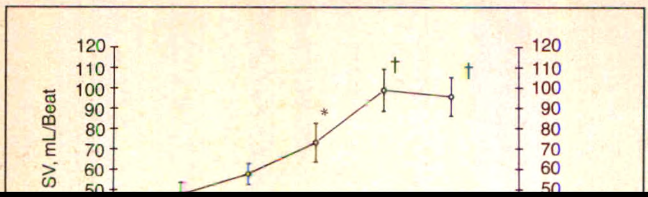

and compliance with total intravascular volume depletion.[31,32] From the present experiments it is impossible to conclude what mechanisms are involved in the sustained elevations of AVP, AII, NPY, and catecholamines.

The role of AVP, AII, NPY, and catecholamines in the fluid-resuscitated burn-injured patient has not been determined. Each of these substances may play an important role

[redacted]

WE DON'T WAIT FOR QUESTIONS ABOUT SUTURE STRENGTH AND HANDLING TO DEVELOP INNOVATIVE ADVANCES.

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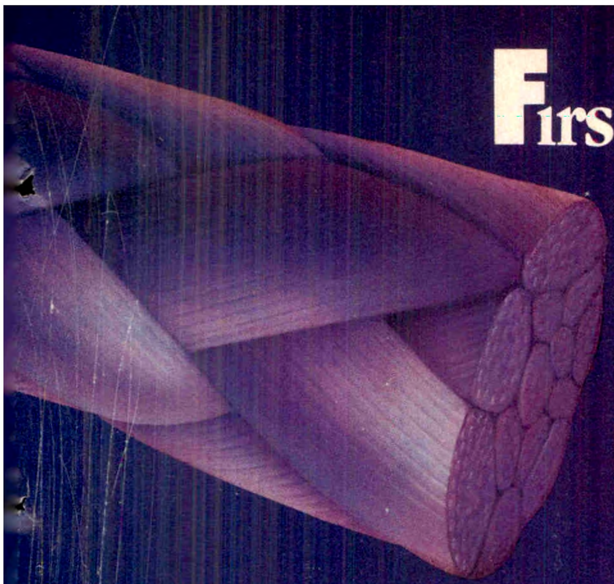
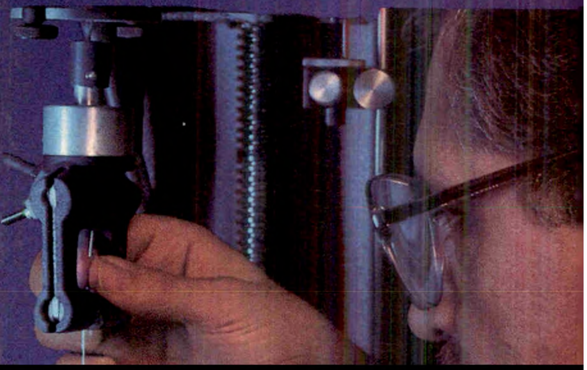


First coated synthetic absorbable suture

Coated VICRYL*
(polyglactin 910) suture,
allows for precise
knot placement and adjustment



First monofilament polypropylene suture

PROLENE* polypropylene suture

[redacted]

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Legends.—*Legends* must be typed double-spaced, beginning on a separate sheet of paper. Length is limited to a maximum of 40 words.

Tables.—Each table must be typed double-spaced, including all headings, on a separate sheet of 8½×11-in paper. Do not use larger-size paper. If a table must be continued, use a second sheet and repeat all heads and stubs. Each table must have a title.

Manuscript Acceptance.—Manuscripts are received with the understanding that they *are not* under simulta-

[redacted]

able only when essential to the message.

News and Announcements.—Brief notices may be submitted of meetings, seminars, or symposiums that are of interest to surgeons.

Acknowledgments.—Illustrations from other publications must be acknowledged. Include the following when applicable: authors, title of article, title of journal or book, volume number, pages, month and year. The publisher's permission to reprint must be submitted to the ARCHIVES when the manuscript has been formally accepted.

[redacted]

Table 1.—Differential Peripheral WBC Counts Following Aerosol Pneumococcal Exposure From rhG-CSF and Sal Solution-Treated Splx and Sham-Operated Mice*

[redacted]

The rhG-CSF, a glycoprotein with hematopoietic effects manifested as a stimulation of progenitor cells leading to production of neutrophils and their immediate precursors, has been shown to increase the count of circulating white

[redacted]

large inocula of bacteria or very virulent bacteria.[25-27] Further experiments are required to explain better whether rhG-CSF has a direct effect by increasing the responsiveness of the local macrophages, or to determine if it is related to an in-

Books

Splanchnic Ischemia and Multiple Organ Failure, edited by Adrian Marston, Gregory B. Bulkley, Richard G. Fiddian-Green, and Ulf H. Haglund, 407 pp, $79, St Louis, Mo, CV Mosby Co, 1989.

The authors note that because of advances in the care of the critically ill, interest has reawakened in the potential of the alimentary tract as a focus of multiple organ failure. This book is presented as a synthesis of the new knowledge and exciting developments in the field that have taken place since the publication of *Intestinal Ischemia* in 1976. The authors include anatomists, physiologists, immunologists, along with physicians and surgeons, all of whom have had considerable interest in splanchnic ischemia.

The book is organized into four sections. Part I covers the normal state of the splanchnic circulation, including the gross and microscopic anatomy, mechanisms of regulation of blood flow and of absorption and insorption, and direct methods of measurement of flow.

Part II covers the causes and effects of disturbances of the normal state. A subsection includes the way mechanical vascular occlusion, vasospasm, and the release of vasopressor materials can affect the gut. Another subsection covers the role of mucosal hypoxia, the effect of oxygen-derived free radicals, of locally released enzymes, and of bacterial products that take place in the gastrointestinal tract as a result of these influences. A third subsection covers the systemic consequences of such pathology abnormality, including the systemic release of endotoxins and myocardial depressant factors, the activation of the arachidonic acid thromboxane pathway, and the role of the damaged bowel in immunosuppression.

Part III deals with clinical syndromes from these mechanisms, including acute and chronic ischemia of the small intestine and ischemic colitis.

Part IV attempts to identify the central role of the gut in the pathogenesis of multiple organ failure. This includes the

the clinical care of the patient with the extended bowel both medically and surgically.

This excellent treatise has succeeded in bringing the latest detailed knowledge of multiple disciplines together to provide the clinician with a better understanding of the mechanisms of and, it is hoped, the prevention and successful treatment of splanchnic ischemia. The final footnote of Adrian Marston so well summarizes the advances of our knowledge of this subject over the past 40 years and will, it is hoped, stimulate the reader to seek answers to some of its unsolved riddles. This book is recommended to all surgeons interested in physiology and particularly the vascular and intensive-care surgeon.

JOHN E. CONNOLLY, MD
Irvine, Calif

Complications in Surgery and Trauma, 2nd ed, edited by Lazar J. Greenfield, 981 pp, $95, Philadelphia, Pa, JB Lippincott, 1990.

This is a very good text. The majority of chapters are well written with excellent references. A particularly strong feature is the wealth of information concerning the incidence of complications in almost all of the chapters. Particularly helpful is the table in chapter 61 for quick reference. Part 4 is a strong section and could serve as a model for future revisions.

Some of the chapters are inconsistent in style. Consistency is obviously difficult to achieve in a multiauthored text and, particularly, with a difficult subject matter such as that of *Complications in Surgery and Trauma.* Nevertheless, some of the better chapters could serve as a framework for style in the next edition. The chapters that give a historical review and evolution of complications, including how treatment has changed over time, are especially interesting. The chapters usually give the pathophysiology of the disease process,

ther operations or disease processes that are found in standard surgical texts. The chapter in which the author gives a standard treatise on the surgical disease or process is poorly constructed; there is no focus on operative or postoperative complications.

Some of the figures are excellent and convey the authors' main points very clearly; figures 2-2, 2-3, and 2-6, are especially illustrative. Other figures, such as figures 5-1 and 6-2, are poorly drawn and are not helpful to the reader. Consistency in the artwork would improve the text.

A minor criticism is the choice of authors in those chapters combining surgery and trauma complications. From the content of the chapters, it was clear that the authors' expertise was in either surgery or trauma, but not both.

Specific critiques of various chapters include the following. In chapter 1 and chapter 32, no mention is made of the Liechtenstein Repair, yet this is increasingly reported with excellent results. I particularly like chapter 4 since it is a treatise on radiation injury written by a surgeon; it is understandable and well written. Chapter 9 lacks any mention of computed tomography or ultrasound drainage of abscesses. Not only are there complications of such techniques, but I believe the authors should have specified certain guidelines for indications of percutaneous drainage. In chapter 12, I would have preferred to see more pathophysiology, particularly regarding renal function tests; this is an area that many surgeons would benefit from in management of their patients in the postoperative period. Chapter 13 does not give an up-to-date critique of the pneumatic antishock garment, its indications, or its limitations. In addition, recent randomized trials are not reported. At least one of these series indicates the garment is harmful in an urban setting. In chapter 14, sepsis is stated to be a direct cause of

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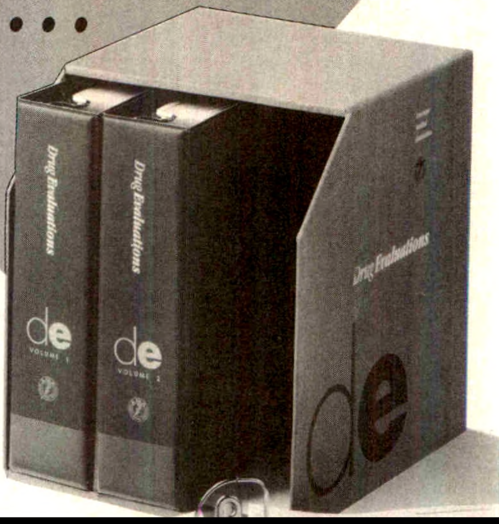

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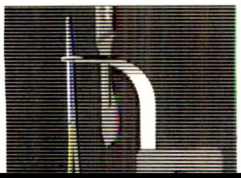

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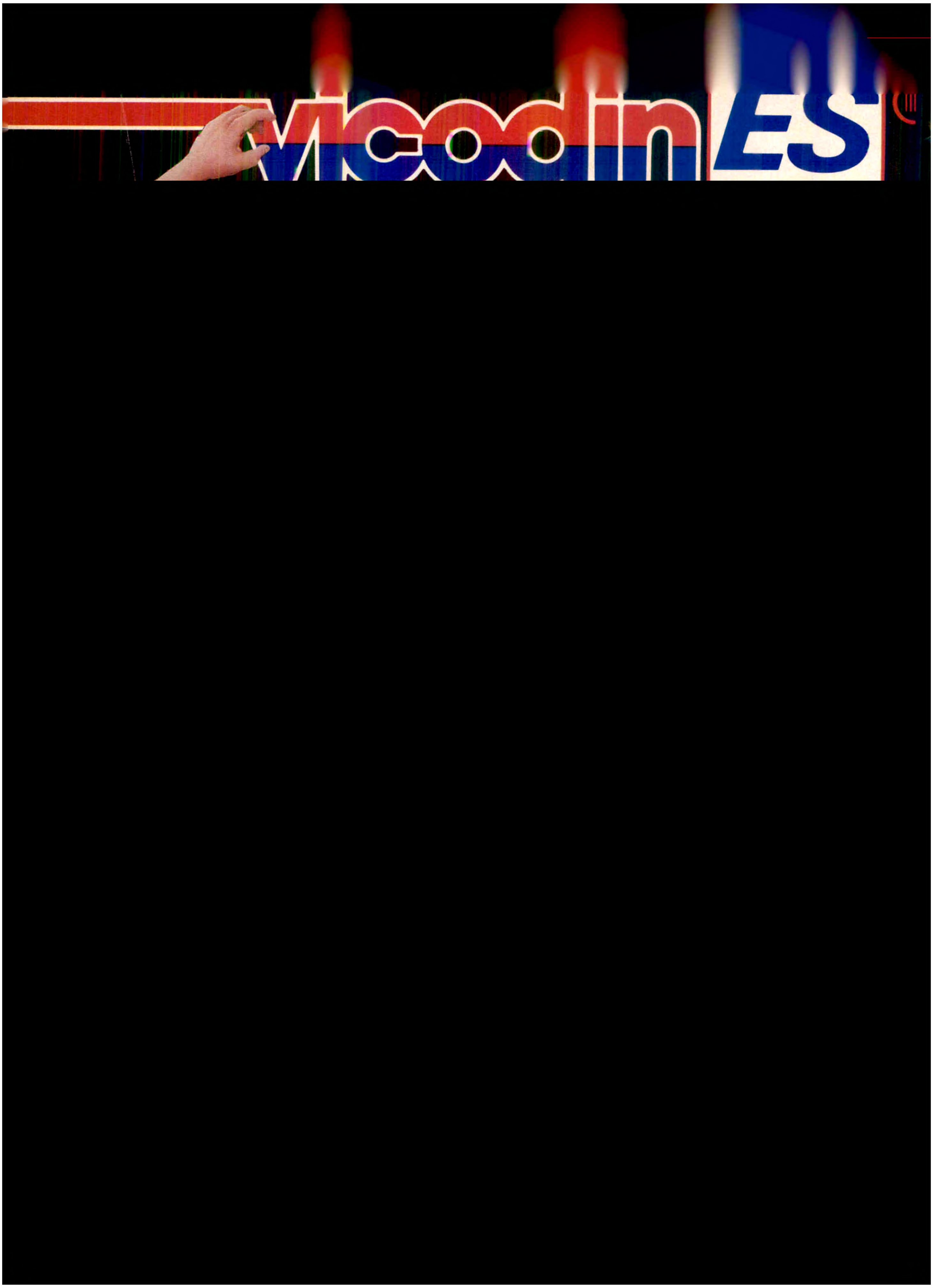

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CONTENTS—Continued

The Potential Contribution of Cardiac Replacement to the Control of Cardiovascular Diseases: A Population-Based Estimate 1148
Thomas E. Kottke, MD; Daniel G. Pesch, MD; Robert L. Frye, MD;
Dwight C. McGoon, MD; Carole A. Warnes, MD; Leonard T. Kurland, MD, Rochester, Minn
- Two thousand one hundred sixty-seven children and 16 500 adults each year could potentially benefit from cardiac replacement.

Invited Commentary: Roger W. Evans, PhD, Seattle, Wash

The Neodymium-YAG Laser and Gastrointestinal Malignancy 1152
Marc L. Eckhauser, MD, Cleveland, Ohio
- The Nd-YAG laser is effective for the palliation of gastrointestinal malignancies.

Differential Production of Interleukin 1 on the Surface of Biomaterials 1158
Tyrone J. Krause, MD; Fredika M. Robertson, PhD; Janice B. Liesch, PhD;
Arthur J. Wasserman, PhD; Ralph S. Greco, MD, New Brunswick, NJ
- mIL-1 was greater by ePTFE adherent cells than mIL-1 produced by cells adherent to SE.

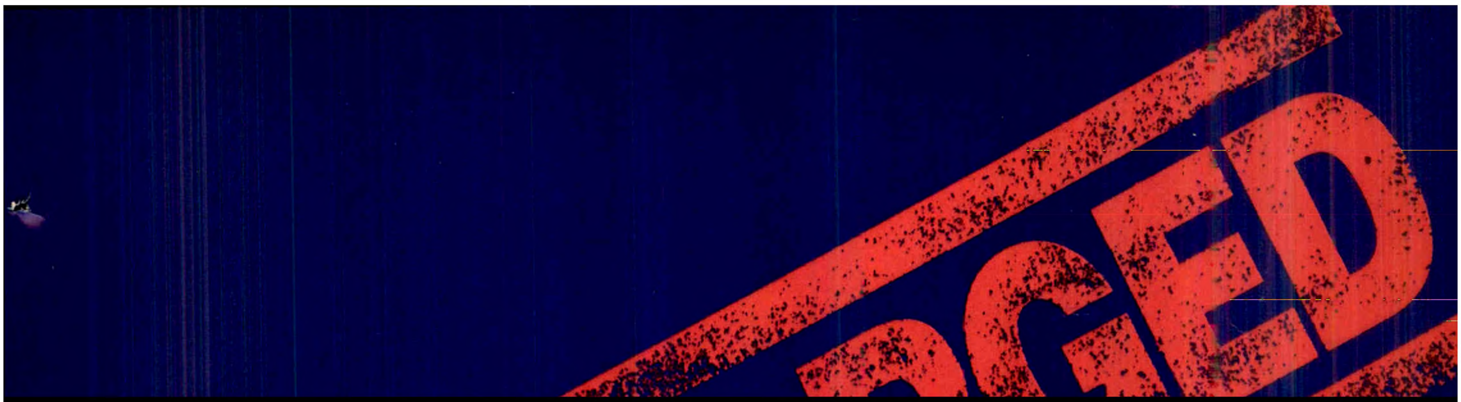
Primary Colorectal Sarcoma 1163
Sybren Meijer, MD; Tamar Peretz, MD; Jeffrey J. Gaynor, PhD; Claire Tan, MS;
Steven I. Hajdu, MD; Murray F. Brennan, MD, New York, NY
- Noncurative treatment and a high-grade tumor were the only prognostic factors favoring tumor-related mortality.

Hepatic Subsegmentectomy With Segmental Hepatic Vein Sacrifice 1170
Makoto Beppu, MD; Takayuki Fukuzaki, MD; Kazuhiro Mitani, MD; Kenichi Fujimoto, MD; Sekizo Taniguchi, MD, Nishinomiya, Japan
- Hepatic subsegmentectomies should be considered for resection of hepatocellular carcinoma when a major hepatic vein is sacrificed.

Invited Commentary: Robert E. Hermann, MD, Cleveland, Ohio

The Effect of Venous Obstruction in Infected Pedicle Flap 1177
Roberta Mann, MD, Brooklyn, NY; Linda G. Phillips, MD; John P. Heggers, PhD; Hugo A. Linares, MD;
Lillian D. Traber, RN; Martin C. Robson, MD, Galveston, Tex

[redacted]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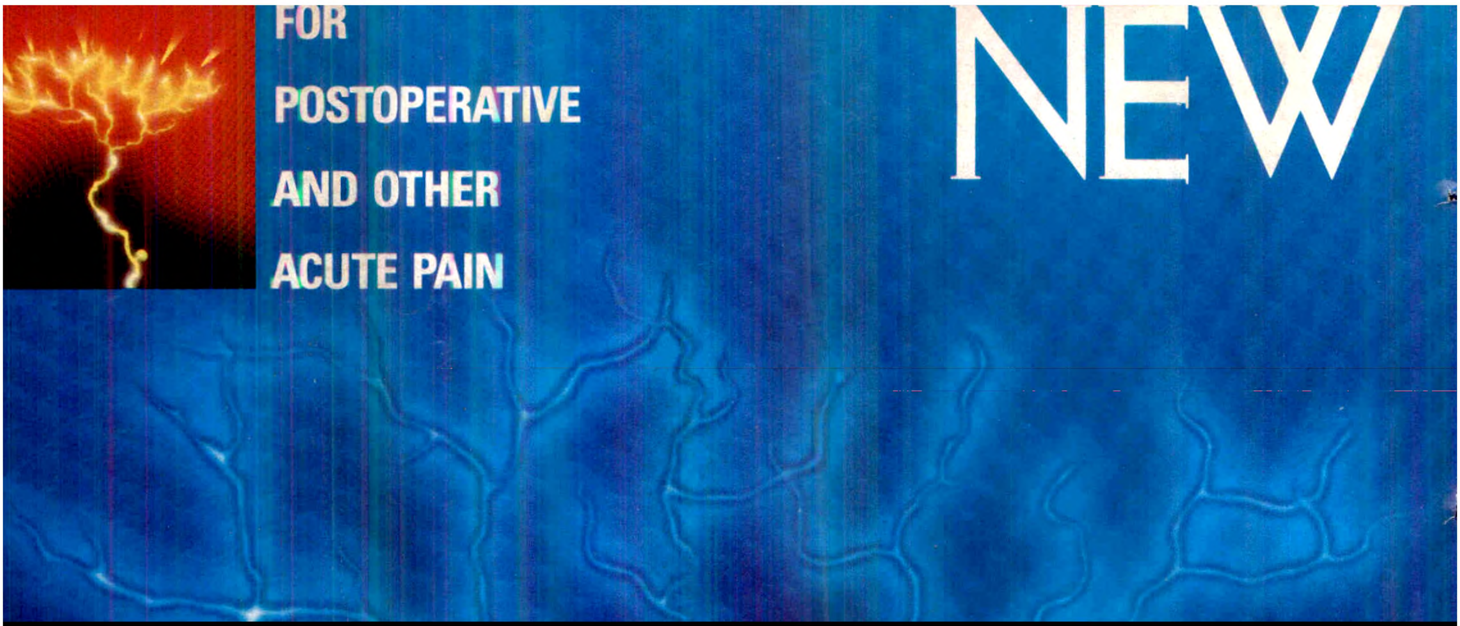

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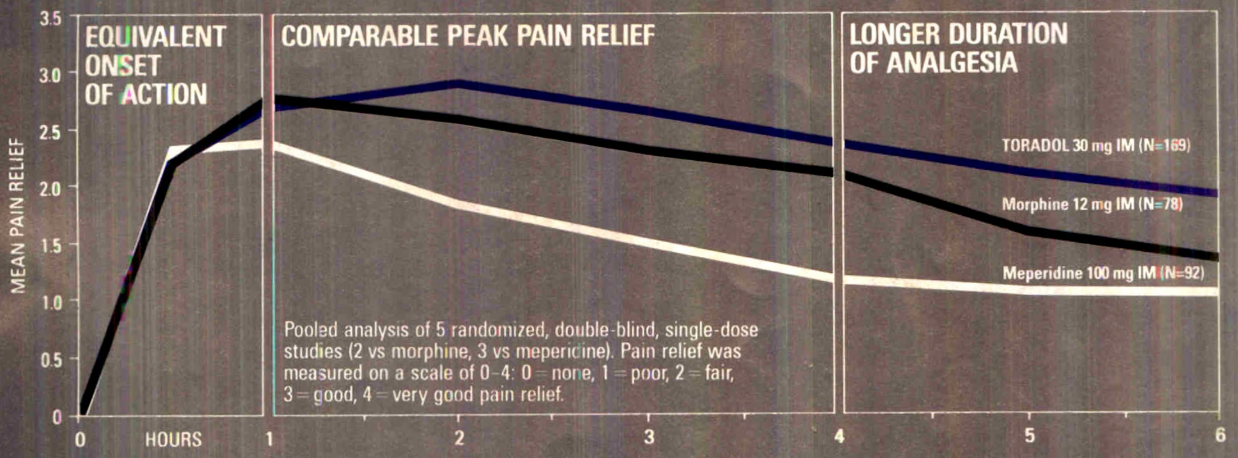

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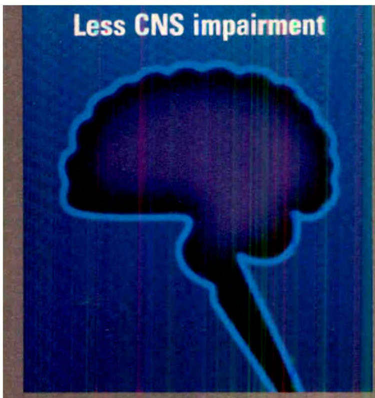

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CONTENTS—Continued

Cystic Teratomas of the Pancreas 1215
Marcelo Mester, MD, Boston, Mass; Hersz J. Trajber, MD, São Paulo, Brazil;
Carolyn C. Compton, MD, PhD, Boston, Mass; Helio S. A. de Camargo, Jr, MD;
Paulo C. Cardoso de Almeida, MD, São Paulo, Brazil; Herbert C. Hoover, Jr, MD, Boston, Mass
- Cystic teratomas of the pancreas are rare, requiring early diagnosis and surgical resection.

Primary Hypertrophic Pyloric Stenosis in the Adult 1219
Robert L. Quigley, MD, Dphil; Scott Pruitt, MD; Theodore N. Pappas, MD; Onye Akwari, MD, Durham NC

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Laboratory Tests: On the first day of therapy with ERGAMISOL/fluorouracil, patients should have a CBC with differential and platelets, electrolytes and liver function tests performed. Thereafter, a CBC with differential and platelets should be performed weekly prior to each treatment with fluorouracil with electrolytes and liver function tests performed every 3 months for a total of one year. Dosage modifications should be instituted as follows: If WBC is 2500-3500/mm^3 defer the fluorouracil dose until WBC is > 3500/mm^3. If WBC is < 2500/mm^3, defer the fluorouracil dose until WBC is > 3500/mm^3; then resume the fluorouracil dose reduced by 20%. If WBC remains < 2500/mm^3 for over 10 days despite deferring fluorouracil, discontinue administration of ERGAMISOL. Both drugs should be deferred unless enough plate-

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Anorexia	2	6
Abdominal pain	2	5
Constipation	2	3
Flatulence	<1	2
Dyspepsia	<1	1
Hematological		
Leukopenia		
<2000/mm^3	<1	1
≥2000 to <4000/mm^3	4	19
≥4000/mm^3	2	33
unscored category	0	<1
Thrombocytopenia		
<50,000/mm^3	0	0
≥50,000 to <130,000/mm^3	1	8
≥130,000/mm^3	1	10
Anemia	0	6
Granulocytopenia	<1	2
Epistaxis	0	1
Skin and Appendages		
Dermatitis	8	23
Alopecia	3	22
Pruritus	1	2
Skin discoloration	0	2
Urticaria	<1	0
Body as a Whole		
Fatigue	6	11
Fever	3	5
Rigors	3	5
Chest pain	<1	1
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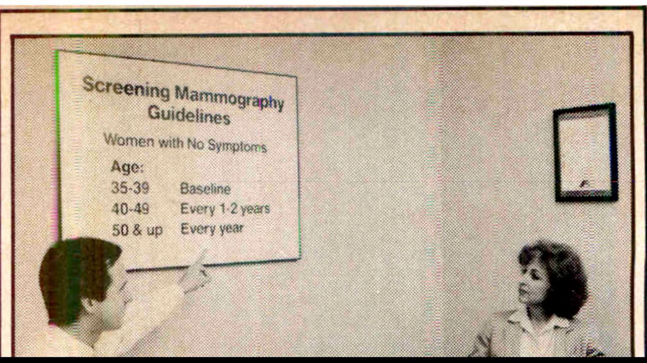

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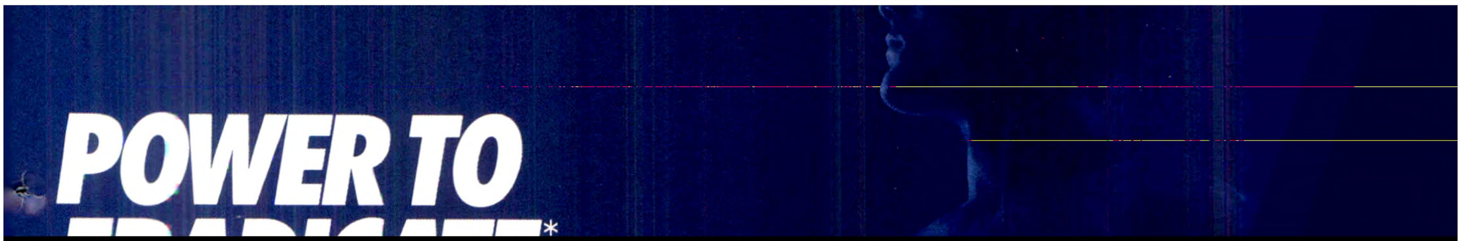

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Commentaries

Evolution of the Healing Room

One of the most significant changes in the care of patients during the past 40 years has been the establishment and proliferation of special care units. Many

[redacted]

than routine ward care after surgery. The answer was to assign a special duty nurse, often hired from a registry, to such cases. The majority of these well-meaning nurses had complex and broad field of medicine. It became obvious that the breadth of this field was such that no one could be

[redacted]

and it is my opinion that the American Board of Surgery would do well to follow this philosophy.

Who Should Be Responsible for Care of the Critically Ill Surgical Patient?

In an article in this issue of the ARCHIVES, Trask and Faber[1] conclude that "surgeons are relinquishing their responsibilities" in the direct care of their critically ill postoperative patients and attribute this trend to several factors. Surgeons may feel uneasy in using the newer mechanical ventilators and other recent advances in intensive care unit (ICU) technology. We can be put at a financial disadvantage if we insist

[redacted]

our training programs, to the point that postoperative management of patients probably occupies more than one half of the time that our residents now spend during their postgraduate educational period. As surgery became a scientific discipline, our researchers focused increasingly on problems in postoperative care, such as those involving postoperative fluid and electrolyte management and postoperative nutrimay appear. The advent of solid-state circuitry and computerlike functions of ICU equipment makes the equipment easi-

[redacted]

daily note) is an excellent way to clarify one's thoughts, even though, in some cases, suggestions for orders might have to

Original Articles

[redacted]

tee with a surgical representative; or (3) other, if none of the previous selections were representative of a particular hospital.

Part 2 of the questionnaire addressed the role of surgeons on staff

[redacted]

noncomplicated ventilator support; (2) placing and using Swan-Ganz catheters for the management of preload, afterload, and contractility; (3) managing complicated postoperative problems requiring compre-

[redacted]

Table 5.—Surgeons' Responsibilities Based on Size of Hospital

	Chiefs of Surgery, %			Nurse Managers, %		
Responsibilities	**Small**	**Medium**	**Large**	**Small**	**Medium**	**Large**
Managing ventilators						

[redacted]

Diagnosis and Treatment of Pancreatic Injuries

An Analysis of Management Principles

David H. Wisner, MD; Rebekah L. Wold, MD; Charles F. Frey, MD

[redacted]

[redacted]

tion and not relied on heavily in diagnosing pancreatic injury. Serial amylase determinations may be more helpful in diagnosis[4,20] and should be done in cases where it has been elected to admit and observe a patient.

Admission and observation with serial abdominal examina-

A number of authors have strongly urged individual ligation of the pancreatic duct after distal pancreatic resection.[2,8,13-15] We have found it difficult to identify the cut end of the pancreatic duct, particularly in the presence of surrounding devitalized pancreas and extensive hematoma after blunt

[redacted]

abscess formation when Penrose drainage was used compared favorably both with the literature and with other types of drainage used in our series.[1-4,6-7,12]

All patients with associated colonic injuries in the series underwent resection and proximal diversion, and we recommend this as the preferred method of management. The vulnerability of the colon when a pancreatic complication occurs is emphasized by the development of colocutaneous fistulas in one patient in spite of diversion and in two other patients without traumatic injuries of the colon.

Both serum amylase and drainage fluid amylase determinations have been proposed as aids in the diagnosis of postoperative pancreatic complications after trauma.[6,11,14] We found neither of them to be very helpful. Serum amylase levels lacked both sensitivity and specificity in predicting complications

[redacted]

our knowledge, this is the first time that an analysis of drainage fluid amylase concentrations after traumatic pancreatic injury has been done.

Drain outputs were not documented well enough in this series to make any definitive comments about the relationship between the volume of output and management of the drain. It would seem logical, however, to exercise caution when drain outputs are more than 50 to 100 mL/d. Our review would indicate that drain amylase concentrations above 100 000 U/L should also prompt a search for pancreatic complications before removal of the drains.

Several authors have urged the routine use of hyperalimentation after resection for pancreatic trauma.[32,33] We found that patients with isolated pancreatic injuries requiring resection often did not require hyperalimentation and were safely fed

Table 1.—Outline of Investigational Protocols*

	SWL+PPC	PCCL
History of biliary colic	Yes†	Yes†
Stones, No.	≤3	No limit
Stone size, mm		
Maximum	30	No limit

antegrade cholecystocholangiogram before removing the catheter. Patients are hospitalized until clinically fit for discharge, which is normally on the first or second postoperative day. Oral antibiotics are prescribed for the first 3 days postoperatively.

RESULTS

To date, with a minimum follow-up of 2 months, six patients have undergone PCCL. Their characteristics are outlined in

[redacted]

Table 3.—Patient Characteristics*

	Patient No./Age, y/Sex					
	1/57/F	2/40/M	3/61/F	4/43/F	5/28/F	6/43/F
Weight, kg	56.3	112.5	99	64.4	65.7	78.8
Major coexisting disease	No	No	Diabetes	No	No	No

[redacted]

Table 4.—Comparative Study of PCCL and Cholecystectomy*

	PCCL (n=6)	Cholecystectomy (n=6)
OR time, h	2.2†	0.8
Postoperative hospital days	1.8	4.5
Meperidine hydrochloride (Demerol), mg	345	1280
Days without food	1.2	3
Days to full activity‡	14.8	21
Complications		
Major	0	0
Minor	1 (17%)§	0

*PCCL indicates percutaneous cholecystolithotomy; OR, operating room. Except for complications, values are means.

†Includes percutaneous access in OR.

‡Subjective data from patient estimates. Several patients with PCCL returned to sedentary work with their catheters draining into a leg bag. All patients were fully active after catheter removal. For patients with cholecystectomy estimate of full activity varied from 14 to 30 days.

§Abdominal pain 30 minutes after catheter removed on 10th postoperative

and has unobstructed biliary drainage. We believe these modifications will minimize the risk of bile peritonitis following catheter removal.

All these new treatment modalities (PPC, SWL+PPC, PCCL) leave the gallbladder in situ, which raises questions regarding the risk of recurrent symptoms and stones. Of all patients undergoing elective cholecystectomy, approximately 5% have persistent or recurrent symptoms.[27,28] In the majority of these, the symptoms are due to retained common bile duct stones and/or other biliary tree conditions, or unrelated disease such as peptic ulceration, hiatal hernia, diverticular disease, and the irritable bowel syndrome.

Stone recurrence after PPC may be as high as 50% within 2 years of withdrawing the medications.[18] The stone recurrence rate after SWL+PPC is unknown but could be similar inasmuch as similar stone populations are involved. The rate of persistent symptoms and stone recurrence after PCCL is unknown but is anticipated to be similar to that after open surgical cholecystostomy. The largest series of patients treated with open cholecystostomy with long-term follow-up is that of Pers and Baden,[29] who followed up 504 patients for an average of 19.7 years. Recurrent calculi were documented in 109 patients (21.6%), of which 86 patients (79%) were symp-

[redacted]

Abdominal Pain in Neutropenic Patients

LCDR David S. Wade, MC, USN; Harold Douglass, Jr, MD; Hector R. Nava, MD; Marion Piedmonte, MA

• The records of 50 patients with abdominal pain and severe neutropenia were retrospectively reviewed to identify factors that may have influenced survival and surgical decisions. Ninety-two percent of these patients had hematologic malignant neoplasms. The patients were divided into four groups: 23 treated nonsurgically who died in the hospital, 10 treated nonsurgically

[redacted]

reviewed to identify patients with neutropenia and abdominal pain. The patients' medical records were then examined to ascertain the age, sex, primary diagnosis, duration of neutropenia, duration of abdominal pain prior to surgical consultation, symptoms and signs of abdominal pain, and diagnostic studies used in their evaluation. The diagnoses of abdominal pain, treatments instituted, and outcomes of

Table 3.—Clinical Diagnoses Among Nonsurgically Treated Patients, With Autopsy Correlation

	Autopsies
[redacted]	[redacted]

Table 5.—Outcome of Treatment of Abdominal Pain in Neutropenic Patients

	Patients Treated With Surgical Exploration		**Patients Treated Without Surgery**	
Variable*	**Survived**	**Died**	**Survived**	**Died**
No. of patients	10	7	10	23
Duration of survival	25 mo (after surgery)	20 d	24 mo (after consultation)	16 d
Average duration of neutropenia, d (range)	15 (3-35)	17 (2-36)	19 (3-31)	22 (4-68)
No. not recovering a WBC count >1.0 × 10^9/L	1	3	0	18
Time between consultation and surgery, d (range)	8 (0-14)	4 (0-9)	. . .	. . .
No. autopsied	. . .	3	. . .	19
Surgically treatable disease	6	3	1	2
Accuracy of clinical diagnosis as confirmed by surgery or autopsy, %	80	71	. . .	42
Neutropenic enterocolitis (clinical diagnosis)	3	3	5	11
Septic death	. . .	5	. . .	19

[redacted]

[redacted]

patients with acceptable morbidity and mortality.[7,9-11]

The decision to operate in the treatment of abdominal pain in neutropenic patients can be exceedingly difficult. It is

[redacted]

the percentage of neutropenic patients who developed abdominal pain at Roswell Park Memorial Institute during the period of this study. Because the average length of time from who died, sepsis was a cause, and 57% suffered from multiple organ system failure. Similarly dismal results of surgical intervention reversing multiple organ system failure have been noted by Norton.[19]

Neutropenic enterocolitis is now a commonly recognized complication of potent combination chemotherapy. Although

[redacted]

in 9. Four patients had pathologic findings consistent with neutropenic enterocolitis; however, none had perforation or transmural necrosis requiring surgical resection. Four patients had normal gastrointestinal tracts. Four of these 9 patients had systemic fungal infections, highlighting the fact that these critically ill patients have many other problems experience gained in our series, we developed the algorithm, displayed in the Figure, which should provide an orderly way to evaluate these critically ill patients and help to identify those patients who require surgical intervention.

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Table 1.—Prehospital Use*

	PTS ≤8, No. (%)	PTS 9-12, No. (%)	Significance	
No. of Patients	44 (31)	100 (69)	. . .	. . .
Age, y	9.4±5.4	12.5±4.5	$t=3.58$	$P\le.0004$
Coma	31 (70)	8 (8)	$\chi^2=60.35$	$P\le.0001$
Airway	21 (48)	5 (5)	$\chi^2=73.41$	$P\le.0001$
Blunt	32 (73)	63 (63)	NS	
Penetrating	8 (18)	30 (30)	NS	

*PTS indicates Pediatric Trauma Score; NS, not significant.

Table 2.—Emergency Department use*

	PTS ≤8, No. (%)	PTS 9-12, No. (%)	Significance	
No. of Patients	44 (31)	100 (69)	. . .	. . .
ED Death	11 (25)	0	$\chi^2=27.07$	$P\le.001$
Admitted to OR	16 (36)	18 (18)	$\chi^2=5.71$	$P\le.017$
Admitted to ICU	17 (39)	9 (9)	$\chi^2=18.139$	$P\le.00002$
Discharged from ED	0	21 (21)	$\chi^2=10.82$	$P\le.001$
LOS, d	27±26	7±8	$t^2=6.03$	$P\le.001$
Hospital death	6 (14)	1 (1)	$\chi^2=10.55$	$P\le.001$

*PTS indicates Pediatric Trauma Score; ED, emergency department; OR, operating room; ICU, intensive care unit; and LOS, length of stay.

Table 3.—Use in Predicting Severity*

	PTS ≤8 No. (%)	PTS 9-12 No. (%)	Significance	
No. of Patients	44 (31)	100 (69)	. . .	. . .
ISS 85	30±22	6±5	$t=10.35$	$P\le.0001$
AIS≥3	43 (98)	39 (39)	$\chi^2=92.98$	$P\le.00001$
3 AIS Groups	9/33 (27)†	2/79 (3)‡	$\chi^2=16.09$	$P\le.00006$
RTS	7±4	12	$t=6.92$	$P\le.00001$

*PTS indicates Pediatric Trauma Score; ISS, Injury Severity Score; AIS, Abbreviated Index Severity Score; and RTS, Revised Trauma Score.

†There were 33 survivors.

‡Seventy-nine patients were admitted.

Table 4.—Pediatric Trauma Score*

	Variables		
	+2	+1	−1
Weight, kg	>20	10-20	<10
Airway	Normal	Maintained	Unmaintained
Systolic BP, mm Hg	>90	50-90	<50
CNS	Awake	Obtunded	Coma
Open wound	None	Minor	Major
Skeletal	None	Closed	Open/multiple
Total Points			

*Circle one variable (+2, +1, −1) from each line and add the scores for the total Pediatric Trauma Score. BP indicates blood pressure and CNS, central nervous system.

RESULTS

(98%) compared with 39% in group B. In addition, there were

[redacted]

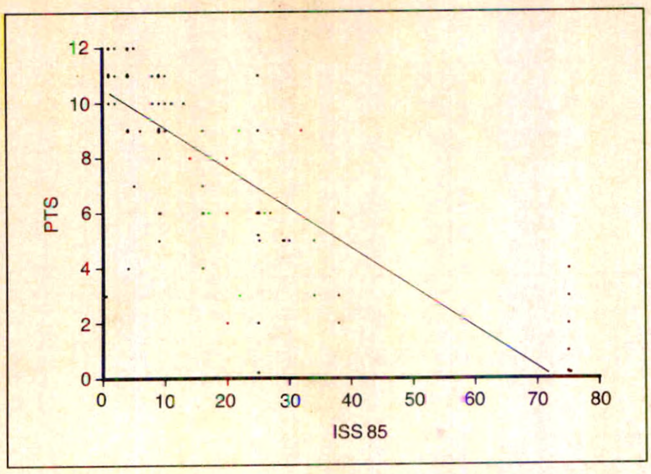

Fig 1.—Correlation of Pediatric Trauma Score (PTS) to Injury Severity Score (ISS) for all patients. Correlation was −.79 ($P<.001$), and slope, −0.15.

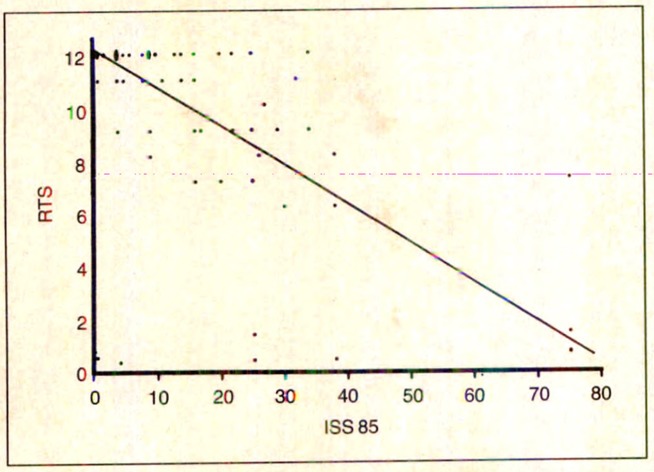

Fig 2.—Correlation of Revised Trauma Score (RTS) to Injury Severity Score (ISS) for all patients. Correlation was −.75 ($P<.001$), and slope, −0.15.

represents the 5 components measured. The PTS and anatomic and physiologic scoring system are the only systems

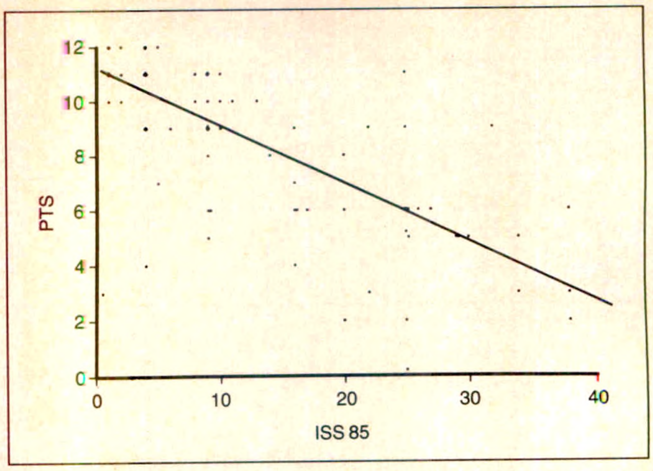

Fig 3.—Correlation of Pediatric Trauma Score (PTS) to Injury Severity Score (ISS) excluding patients with Abbreviated Index Severity scores equal to 6. Correlation was −.73 ($P<.001$), and slope, −0.21.

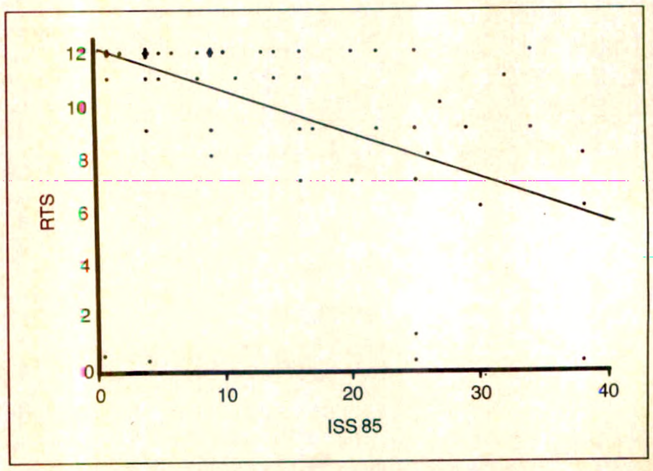

Fig 4.—Correlation of Revised Trauma Score (RTS) to Injury Severity Score (ISS) excluding patients with Abbreviated Index Severity scores equal to 6. Correlation was −.50 ($P<.001$), and slope, −0.13.

sustained a major penetrating injury or multiple fractures. Since the PTS of 9 can quickly be identified, any other abnor-

[redacted]

instance remains a useful tool. Whether the different slopes (Figs 1 and 3) will be useful in evaluating the EMS system remains to be proved. Utilizing advanced life support procedures to identify severity may not be as sensitive as the PTS.

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Peritoneal Lavage in Abdominal Sepsis

A Controlled Clinical Study

Moshe Schein, MD, FCS(SA); Gary Gecelter, MB, BCh; Wolf Freinkel, MB, BCh; Herman Gerding, MB, BCh†; Piet J. Becker, PhD

[redacted]

chronic ulcers in good-risk patients were treated by definitive ulcer procedures. Small-bowel perforations were closed primarily or resected and anastomosed; colonic perforations were treated by resection without a primary anastomosis. All wounds were closed primarily; neither incisional drains nor topical antibiotics or antiseptics were used. Intraperitoneal drains were placed only when abscesses were found.

All patients received systemic antibiotics: penicillin G potassium,

Table 1.—Source of Peritoneal Contamination and Mortality*

	Group 1		Group 2		Group 3		Total	
Source†	**No.**	**Died**	**No.**	**Died**	**No.**	**Died**	**No.**	**Died**
Perforated DU	4	1 (25)	8	1 (12.5)	13	2 (15)	**25**	**4** (16)
Perforated GU	7	1 (14)	8	1 (12.5)	6	1 (17)	**21**	**3** (14)

[redacted]

Table 3.—APACHE II Score and Mortality*

	APACHE II Score									
	0-10		11-15		16-20		21-25		26-30	
Group	**No.**	**Died**	**No.**	**Died**	**No.**	**Died**	**No.**	**Died**	**No.**	**Died**
1	20	1	4	2	4	2	1	1	0	0
2	19	0	4	1	1	1	3	2	2	2
3	18	1	9	1	0	0	1	1	0	0
Total†	**57**	**2** (4)	**17**	**4** (24)	**5**	**3** (60)	**5**	**4** (80)	**2**	**2** (100)

*APACHE indicates acute physiologic and chronic health evaluation.
†Data in parentheses are given as the percent mortality.

Table 4.—Surgical and Medical Complications in the Various Groups

	Group 1	Group 2	Group 3	Total

neal abscesses were identical in both groups. Wound infections, however, were twice as common in the group that received IOPL with saline solution. Also, in this trial, routine perioperative systemic antibiotics were omitted.[17] Silverman et al[18] compared IOPL with tetracycline with that with saline

[redacted]

the score subgroups was not identical: while five and six patients in groups 1 and 2, respectively, belonged to the subgroup with an APACHE score greater than 15, which carried a mortality of 75%, only one patient in group 3 had such a high score. We believe therefore that the reduced mortality rate in group 3 cannot be attributed to the IOPL with chloramphenicol but resulted either by chance or from the lesser severity of illness in patients belonging to that group.

The wound infections rates in the three groups were identi-

cluding wound protection and greater attention to the prevention of intra-operative soiling, or differences in the populations studied, may be responsible.

This study deals with a relatively small number of patients, thus a statistical type II error is possible. Furthermore, patients with severe forms of IAIs (postoperative, diffuse fecal, and infected pancreatic necrosis) were not included; it is possible that because of their omission, we failed to show the benefit of IOPL. Nevertheless, we can conclude that, in our experience, during a period of 2 years, IOPL with saline

[redacted]

Occlusive Dressings

[redacted]

deposited into a sterile glass cylinder that surrounded the wound. The inoculum was scrubbed into the wound by using a Teflon spatula.

Recovery Methods.—For each strain, culture methods of recov-

[redacted]

stained and presumptively identified to assure that the inoculation strain was being quantitated. The presumptive identification test for each pathogen was as follows: *S aureus*, the ability to coagulate rabbit

[redacted]

COMMENT

In this study, known wound pathogens with different oxygen requirements were inoculated into superficial wounds in domestic pigs. Three physically distinct dressings that differed considerably in their oxygen permeability were applied to the wounds immediately after inoculation. Control wounds were inoculated but left open to the air. Quantitative bacterial cultures were obtained at 24, 48, and 72 hours.

[redacted]

low levels. DuoDERM was slightly less able to support *P aeruginosa* growth than were the other dressings. Katz et al[8] also found low values for *P aeruginosa* growth beneath DuoDERM. They ascribed the lower values to DuoDERM's ability to absorb moisture, creating a dry environment that is less favorable for *P aeruginosa* growth. In addition, DuoDERM is oxygen impermeable and probably creates a lower than optimal oxygen microenvironment. Based on the studies of *B*

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The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® Injection/Zantac® Injection Premixed product labeling.
INDICATIONS AND USAGE: Zantac® Injection and Zantac® Injection Premixed are indicated in some hospitalized patients with pathological hypersecretory conditions or intractable duodenal ulcers, or as an alternative to the oral dosage form for short-term use in patients who are unable to take oral medication.
CONTRAINDICATIONS: Zantac® Injection and Zantac® Injection Premixed are contraindicated for patients known to have hypersensitivity to the drug.
PRECAUTIONS: General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.
3. In controlled studies in normal volunteers, elevations in SGPT have been observed when H_2-antagonists have been administered intravenously at greater than recommended doses for five days or longer. There-

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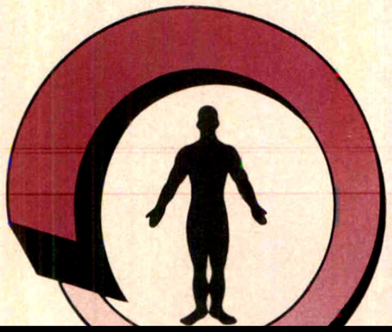

Approaches to the Treatment of Surgical Infections in the 90's

[redacted]

were followed up for at least 24 months. There were 14 deaths, including 12 in patients who had metastatic disease. The average age of the 259 patients studied was 50.5 years (range, 26 to 83 years). Clinical staging was available for 256 of the patients. Clinical axillary node involvement revealed 217 patients (84%) as N0 (no clinical suspicion of axillary involvement) and 36 patients (14%) as N1 (clinically suspicious). Of the N0 patients, 143 (66%) were T1, 70 (32%) were T2, and 4 were T3 (2%). Estrogen receptor status was positive in 48.4%, negative in 17.7%, and unknown in 33.8%.

Surgical Technique

The patient was placed under general anesthesia and positioned supine on the operating table with her arm positioned at a right angle to her body. A transverse incision approximately 4 to 6 cm was made at the inferior portion of the axillary hairline from about 1 cm below the pectoralis major to the level of the latissimus dorsi. This was sharply dissected down through the axillary fascia.

After identification of the lateral border of the pectoralis major, the medial pectoral nerve to this muscle was identified and preserved. A lighted retractor was then placed under both the pectoralis major and minor, and the axillary tissue was swept laterally, thus clearing out [redacted]

reapproximated, and the subcutaneous tissue was closed with an absorbable suture. The skin was closed with a subcuticular stitch, with an adhesive closure (Steri-strips) added.

Operating time averaged approximately 1 hour, and the estimated blood loss was less than 50 mL. Postoperatively, patients were given no restrictions to arm mobility and in fact were encouraged to move their arms to prevent any stiffness.

Radiation Technique

Nearly all patients received their therapy at the Joint Center for Radiation Therapy, and the details of the treatment have been presented elsewhere.[8] There was some evolution in the volume and doses of radiation therapy employed during the study period. The vast majority of patients underwent radiation therapy restricted to the breast and received 4500 to 4600 cGy in 23 to 25 fractions over 5 weeks and additional radiation ("boost") to the primary site by electron beam for a total dose of 6100 cGy.

RESULTS

Table 1 shows the likelihood of finding histologic evidence of

[redacted]

sampling and radiation therapy had a 9.1% incidence of lymphedema as compared with a 7.4% incidence with axillary clearance alone. In our series, the axillary vein was identified, but the dissection of the axillary fat pad was begun just inferior to the vein. There was no "stripping" of this vessel. This technique was found by Kissin et al to be significant in reducing subsequent lymphedema.

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[redacted]

Table 1.—Number of Deaths by Cause, Olmsted County, Minnesota, 1979 to 1983

	All Causes	Cardiac Only

Table 2.—Disposition of Potential Candidates Younger Than 15 Years

Age at

[redacted]

Table 3.—Classification of Potential Candidates 15 to 69 Years Old

Condition	No.
Sudden death alone	128
Sudden death and comorbid conditions	49
Comorbid condition alone	34
Insufficient information	2
Candidate for cardiac replacement	35
Total	**248**

Table 5.—Comorbid Conditions Leading to Exclusion in the Population 15 to 69 Years Old

Associated Disease	Sudden Death	Nonsudden Death
Consent and compliance contraindications		
Alcoholism and effects of alcoholism	10	3
Mental retardation	2	0
Senile dementia	1	1
Noncompliance	2	0
Nonconsent	0	1
Neurologic disease		

[redacted]

finally accepted as candidates also had milder comorbid conditions. Ignoring comorbidity would double the size of the adult candidate pool, and excluding all individuals with comorbid conditions would reduce the size of the pool by 50%. While patients up to the age of 69 years were considered as potential

This investigation was supported in part by grant HL 24326 from the National Institutes of Health.

The stimulus for this work arose from the participation of Drs McGoon and Frye in the working group of the National Heart, Lung, and Blood Institute on the Artificial Heart. The members of the entire working group gave encouragement in pursuing this study, particularly the chairman of the working group,

[redacted]

Table 1.—Dysphagia Grading Scale

Grade	Description
1	Able to swallow all solids without difficulty
2	Difficulty swallowing some hard solids, but able to swallow

Table 2.—Summary of Patient Characteristics (N = 37)

	Malignant Neoplasm		
	Esophageal (n = 20)*	Gastroduodenal (n = 5)†	Colorectal (n = 12)‡

[redacted]

firmed the efficacy and reduced morbidity of Nd-YAG laser therapy for obstructive esophageal carcinoma.[12-14] All of the patients in our group failed to benefit from prior radiotherapy and chemotherapy. Although luminal patency was restored in all patients, a successful, functional outcome was less apparent in those individuals with proximal lesions, as reflected by their dysphagia scores, which were probably secondary to tumor infiltration of the upper esophageal sphincter.

There were no perforations or other laser-related complica-

since no large series exists. In this study, both patients were able to tolerate either a soft or regular diet.

There is a subset of patients with colorectal disease who will initially present with overwhelming metastatic or locally unresectable disease. This group represents anywhere from 8.5% to 30% of patients admitted for this disease.[15] The symptoms of obstruction, hematochezia, and tenesmus have, in the past, been treated with either radiation, palliative resection, colostomy, or a combination thereof. Laser recanalization for

[redacted]

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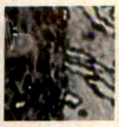

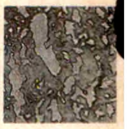

Biocompatibility of an implanted material encompasses not only

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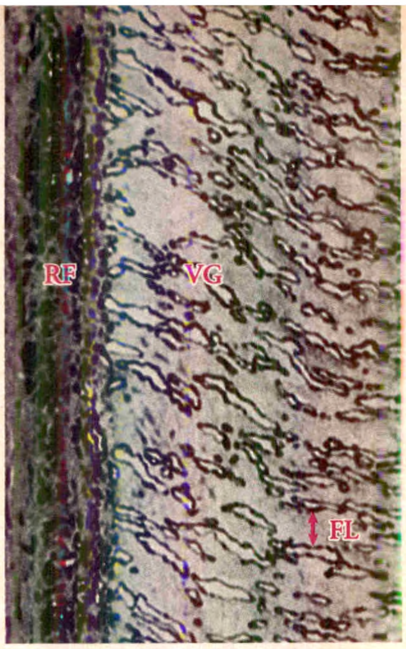
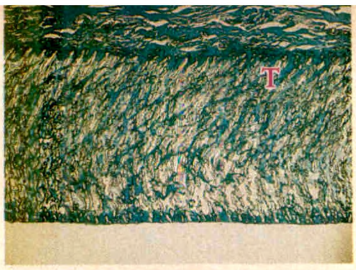
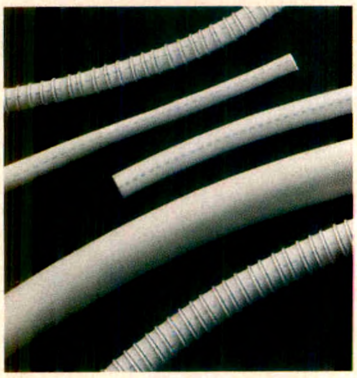
GORE-TEX® VASCULAR GRAFT

For vascular applications, surgeons requested a porous tube that did not need preclotting, would not become aneurysmal and to which tissue would readily attach with penetration of fibroblasts and other cells into the material. In 1975 Gore introduced an expanded PTFE reinforced vascular graft (VG). With an average fibril length (FL) of 25 microns, the porous graft implant is incorporated by surrounding tissue (T). The microstructure does not necessitate preclotting and the unique expanded PTFE reinforcing film, (RF) integral with the graft outer surface, prevents aneurysmal dilatation, enhances suture retention and prevents "zippering" without inhibiting cellular penetration.







Trichrome (left) and silver stained (far left) thin sections of a GORE-TEX Vascular Graft explanted from the femoropopliteal position at 4½ years. Tissue is firmly attached to the graft. The dilatation-resistant reinforcing film permits ingrowth of cells and collagen production within the graft wall. (Trichrome 40X and Silver Stain 150X)

GORE-TEX® CARDIOVASCULAR PATCH

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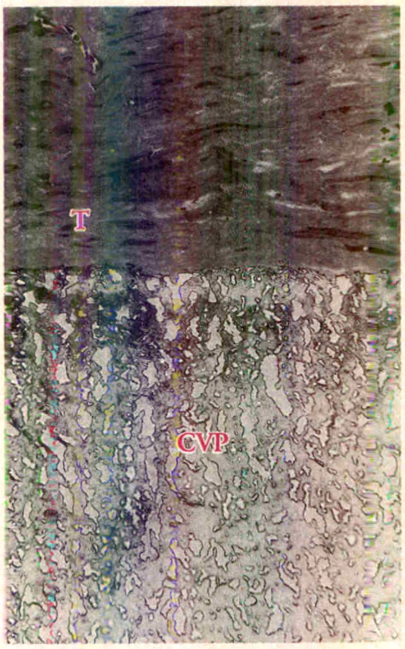
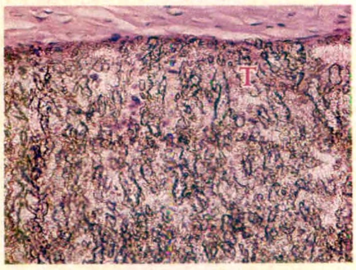
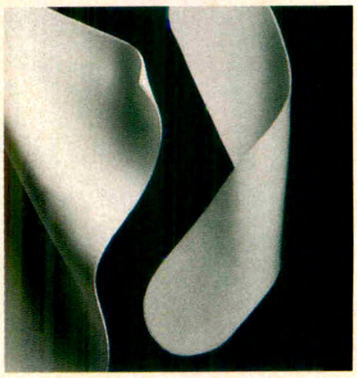


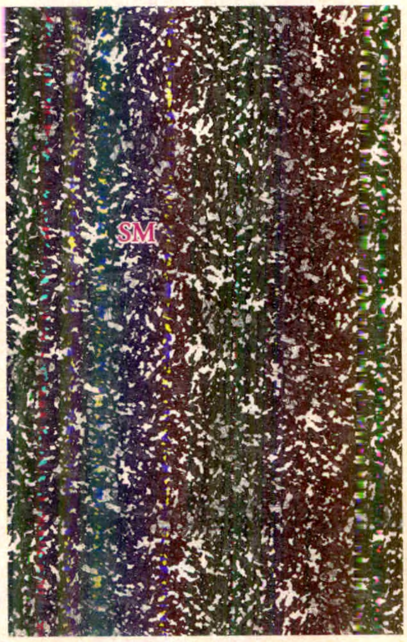


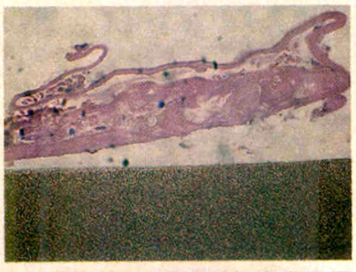


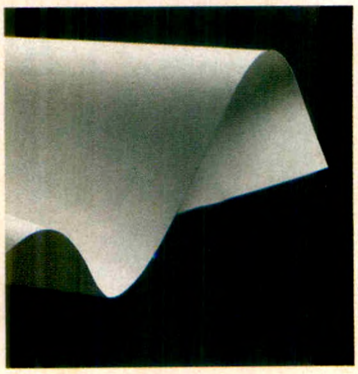
H & E (left) and silver stained (far left) thin sections of a GORE-TEX Cardiovascular Patch explanted from the canine abdominal aorta at 6 months. Tissue response to the patch and graft (above) is the same. (H & E 75X and Silver Stain 170X)

GORE-TEX® SURGICAL MEMBRANE

The challenge of preventing epicardial adhesions following coronary bypass or open-heart procedures was met by altering the basic node-fibril microstructure of GORE-TEX expanded PTFE to exclude cells. The resultant GORE-TEX Surgical Membrane material (SM), with documented successful clinical use since 1975, provides an effective plane of dissection with minimal adhesions. The combination of smooth surface and microporous structure limits adherence of adjacent tissue structures.

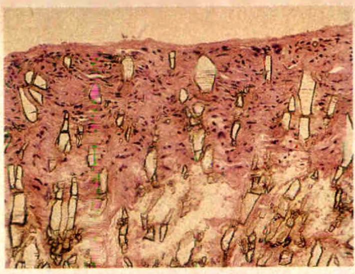


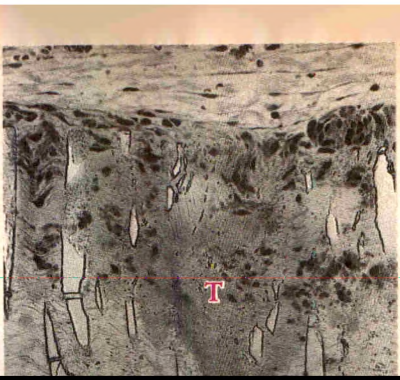




H & E (left) and silver stained (far left) thin sections of a GORE-TEX Surgical Membrane used for pericardial closure explanted from a patient at 3 months. The limited tissue attachment provided an easy plane of dissection with minimal epicardial scarring. (H & E 160X and Silver Stain 1340X)

H & E (right) and silver stained (far right) thin sections of GORE-TEX Soft Tissue Patch explanted from a ventral hernia repair site at 4 years. The multi-directional porous microstructure permits incorporation of the material by the tissue (T) at the





GORE-TEX® SOFT TISSUE PATCH

Hernia repairs (inguinal, ventral, and other), chest wall reconstructions, and other soft tissue defects require a soft, flexible, porous flat sheet material with multiaxial strength that can withstand suture line stresses during exertion, such as coughing or lifting. The GORE-TEX Soft Tissue Patch (STP), with a fibril length the same as that of

Differential Production of Interleukin 1 on the Surface of Biomaterials

Tyrone J. Krause, MD; Fredika M. Robertson, PhD; Janice B. Liesch, PhD; Arthur J. Wasserman, PhD; Ralph S. Greco, MD

• The production of cytokines on the surface of surgical biomaterials plays a major role in their biocompatibility. Membrane-associated interleukin 1 (mIL-1) is a cytokine found on the surface of macrophages activated by biomaterials. To better understand the host–foreign body interaction, we quantitated the production of mIL-1 on the surface of two materials commonly used in surgery, expanded polytef (ePTFE) and silicon elastomer (SE). The mean (±SD) level of mIL-1 produced by adherent cells to ePTFE significantly decreased from day 2 (13 746±3630 cpm per disk) compared with day 7 (2828±1304 cpm per disk). However, the level of mIL-1 produced by ePTFE-adherent cells was still markedly greater than the level of mIL-1 produced by cells adherent to SE (1877±1028 vs 1595±822 cpm per disk). These results indicate that ePTFE and SE elicit a differential host response in terms of cytokine production. This study may enhance our understanding of the cellular events on the surface of biomaterials that underlie clinical observations.

(*Arch Surg.* 1990;125:1158-1160)

Biomaterials elicit both an acute and chronic inflammatory reaction.[1,2] The host response to a specific biomaterial is largely dictated by the surface properties of the prosthetic device.[1,3,4] The tissue macrophage is the major cell type found on the surface of foreign materials.[1] These cells produce various biologic mediators that participate in the immune and inflammatory responses,[5] such as interleukin 1 (IL-1). This cytokine is produced by activated macrophages and functions as a potent stimulant of other cells in the healing and repair process.[6] Interleukin 1 is produced in both soluble and membrane-associated forms.[7,8] Soluble IL-1 has been found to be produced by macrophages that were differentially activated on adherence to various commonly used biomaterials.[9,10] This secreted form of IL-1 is quantitated in the inflammatory exudate. The surface-associated IL-1 (mIL-1) can be measured in the leukocyte membrane.[7] Although mIL-1 has a number of functions in common with its soluble counterpart, it may also act as a local stimulant to other cells adherent to the surface of the biomaterial. In addition, the expression of mIL-1 may be temporarily dissociated from, and persist longer than, that of soluble IL-1. It is our hypothesis that mIL-1 adherent to the surface of biomaterials is produced in quantities that are dependent on the structure and composition of the material. Using expanded polytef (ePTFE) and silicon elastomer (SE), two commonly used prosthetic materials in surgery with markedly different surface properties, we quantitated mIL-1 produced by leukocytes adherent to the biomaterial surface. We also compared the structure of the cells adherent to these polymers to determine their state of activa-

MATERIALS AND METHODS

Biomaterials

Medical grade ePTFE (lot 885850, Bard Implants Division, Billericka, Mass) and SE sheeting (lot HH066502, type 500-7, Dow Corning Corp, Midland, Mich) were used. The materials were standardized as to size and shape by cutting disks of 0.5-cm diameter with a cork borer. They were autoclaved at 121°C and 15 psi for 15 minutes.

Air Pouch

The rodent air pouch was produced as previously described.[11] Briefly, male Sprague Dawley rats (200 g, Jackson Laboratory, Bar Harbor, Me) were anesthetized with ether, and 20 mL of prefiltered air was injected subcutaneously into the dorsal area using a 25-gauge needle. This formed an air pouch that was kept inflated by reinjecting air every 2 days if necessary, taking care not to stretch the pouch wall by overinflation. By 7 days, the pouch lining was mature and now resembled a synovial lining, composed mainly of macrophages and fibroblasts.

The rats were again anesthetized with ether, the pouch was shaved and wiped once with 95% alcohol, and then a 1-cm incision was made in the skin that exposed but did not cut into the pouch lining. Using sterile technique, the air pouch was opened with a No. 11 blade, and eight implants of either ePTFE or SE were placed inside. The wound was closed with staples and the pouch reinflated. This technique minimized bleeding into the pouch. At 2 or 7 days, the rats were killed with ether and, under sterile conditions, the implants were removed and immediately prepared for assay. Representative samples from each group were cultured in agar plates to detect bacterial contamination. There were six rats in each group.

mIL-1 Assay

Using ePTFE and SE as the biomaterials, we quantitated the expression of mIL-1 by adherent cells at both 2 and 7 days. The implants were removed and immediately fixed with 1% paraformaldehyde for 15 minutes at 37°C according to the procedure described by Kurt-Jones et al.[7] After fixation, the implants were placed in 96-well microtiter plates (Nunc, Thousand Oaks, Calif) containing RPMI 1640 medium (Gibco, Grand Island, NY) supplemented with 10% fetal calf serum (Hazelton Co, Lenexa, Kan), 2 mmol/L of L-glutamine, 5 mmol/L of HEPES, 50 μmol/L of 2-mercaptoethanol, 100 μg of streptomycin, and 100 U of penicillin per milliliter and incubated overnight. The mIL-1 activity was assayed by adding the T-cell clone D10.G4.1 (2×10^4 cells) and 2.5 μg of concanavalin A (Sigma Chemical Co, St Louis, Mo) to each well of the 96-well microtiter plate. After 48 hours' incubation at 37°C, the D10.G4.1 cell proliferation was assessed by measuring the tritiated thymidine incorporation (0.5 μCi per well) for 18 hours. The cells were harvested with a cell harvester (PHD, Cambridge Technologies, Cambridge, Mass) and the radioactivity was measured in counts per minute using a liquid scintillation

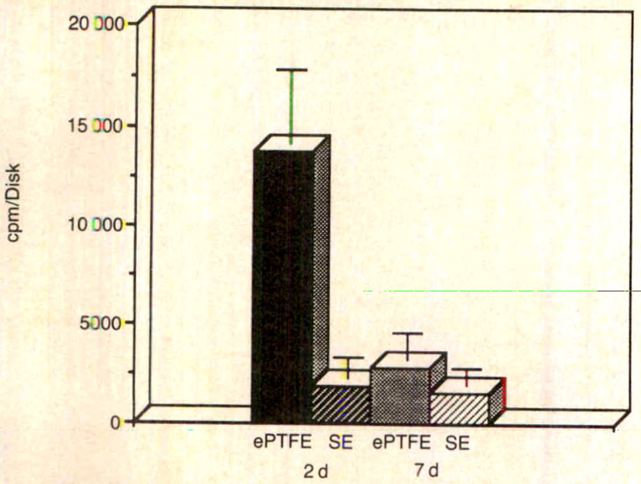


Fig 1.—The level of membrane interleukin 1 (mIL-1) synthesized by the adherent cells was assessed utilizing the highly sensitive D10.G4.1 proliferation and tritiated thymidine incorporation assay. The quantity of mIL-1 produced from the surface of expanded polytef (ePTFE) was significantly greater than that from the surface of silicon elastomer (SE) at both 2 and 7 days (*P*<.001, *P*<.05, respectively).

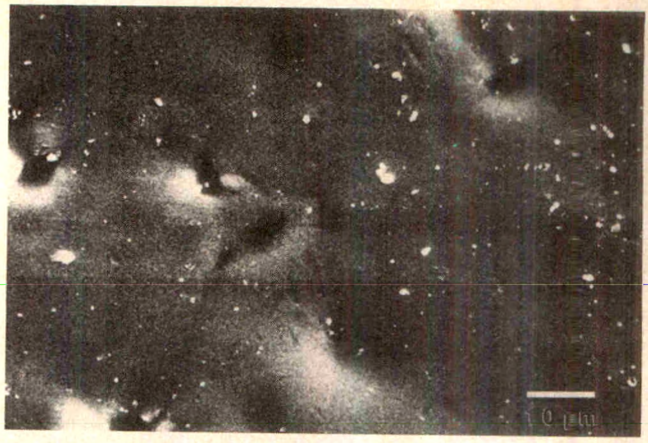
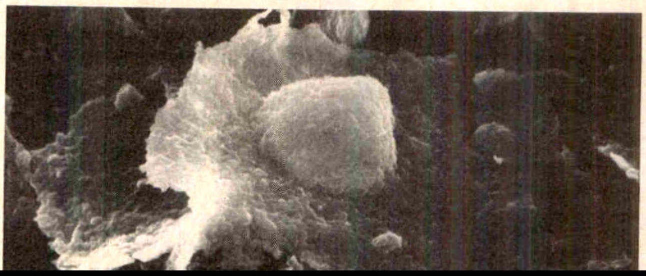
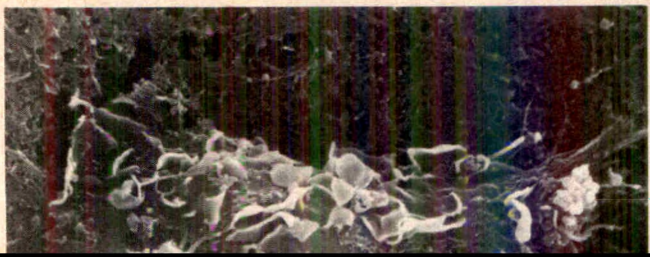


Fig 2.—Control surface of silicon elastomer.

crose(pH 7.4) for 48 hours at room temperature. They were then postfixed for 30 minutes in 1% osmium tetroxide and poststained in 1% uranyl acetate for 1 hour at 25°C. The samples were dehydrated,





to the demise of the macrophages on the surface of Biomer (silicon elastomer).

In the present study, scanning electron microscopy was used to examine the morphologic alterations by cells. Based on the scanning electron microscopy observations, we determined that there were greater numbers of cells present on SE. The cells on the surface of SE were characterized by a smooth surface with minimal cytoplasmic spreading. These changes are characteristic of epithelial or fibroblastlike cells.

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procedure was performed in 10 patients with a colonic primary tumor. Among the 32 patients who underwent curative resection, adjuvant postoperative chemotherapy and radiotherapy were administered to three and two patients, respectively. Thirteen patients underwent palliative therapy, chemotherapy only (n=8), radiotherapy only (n=2), or both (n=3). No objective partial or complete remissions were noticed.

Pathologic Characteristics

The tumor size varied from 2 to 30 cm in maximum diameter. Large tumors often tended to be lobulated, with central necrosis, hemorrhage, and cavitation.

Histologic grading of the sarcomas was based on differentiation, cellularity, amount of stroma, vascularity, amount of necrosis, and the number of mitoses, and the tumors were divided into low- and high-grade tumors.[13] The size of the tumor was recorded as less than 5 cm or 5 cm or larger. Of the 50 sarcomas, 49 were diagnosed as leiomyosarcoma and one as hemangiopericytoma. In 30 cases the primary tumor was classified histologically as a high-grade tumor, in 14 cases as a low-grade tumor, and in six cases the grade could not be determined due to unavailability of some of the older archived material. In 35 cases the sarcoma measured more than 5 cm in diameter, in 12 cases smaller than 5 cm, and the size was unknown in three cases. The hemangiopericytoma was located in the descending colon and was histologically high-grade and larger than 5 cm.

Table 1.—Distribution of Clinicopathologic Characteristics

No. of patients	50
No. of men/No. of women	32/18
Age, y	
Median	57.5
Range	18-86
Site of primary tumor, No. of patients	
Right colon	7
Transverse colon	2
Left sigmoid colon	8
Unknown	1
Rectum	32
Anterior wall	10
Posterior	7
Lateral	6
Circular	1
Unknown	8
Histologic type, No. of patients	
Leiomyosarcoma	49
Hemangiopericytoma	1
Mode of treatment by tumor site, No. of patients	
Rectum	
Abdominoperineal resection	15
Local excision	12
Biopsy only	4
Unknown	1
Colon	
Colectomy	14
Biopsy only	4

Lymph node metastasis was shown to be present in six cases (12%) at diagnosis. A surgical specimen after a colectomy or abdominoperineal resection to study the regional lymph nodes was obtained in 29 cases, and four of these patients also had distant metastasis at the time of diagnosis. The lymph node metastases at presentation were found exclusively in the high-grade leiomyosarcomas.

Statistical Methods

A most important set of prognostic factors for the rate of death due to the disease (ie, tumor mortality) was determined using the Cox model stepwise regression technique[14] in the BMDP statistical package.[15] Univariable log-rank and stratified log-rank tests[16] were performed, and Kaplan-Meier curves[17] were used to display covariate effects. Four patients who died of unrelated causes were excluded. The Cox model stepwise regression technique was also used to identify prognostic factors for (1) the rate of development of distant metastasis following treatment for localized disease and (2) the rate of death following the development of (or presentation with) distant metastasis. Characteristics associated with death due to progressive local disease were considered without a formal analysis because there were few deaths of this type. Associations among the important prognostic factors were evaluated using Pearson (uncorrected) χ^2 tests.

RESULTS

Tumor Mortality

A Kaplan-Meier tumor mortality curve for the entire group of 50 patients shows the estimated median survival to be 33 months. The initially steep descent diminishes beyond that time.

Prognostic factors associated with the rate of death due to the disease are presented in Table 2. Palliative treatment, presentation with metastasis, high-grade tumor, tumor larger than 5 cm, and colonic site were associated, in a univariable analysis, with an unfavorable outcome. Figure 1 shows that the 17 patients who underwent noncurative treatment had a significantly higher rate of death due to the disease ($P<.00001$). The estimated median survival in the curatively and noncuratively treated groups was 175 and 12 months, respectively. Presentation with metastatic disease implied a significantly less favorable prognosis ($P<.00001$). Figure 2 displays a significantly higher rate of tumor mortality in patients with a high-grade tumor ($P=.0003$); the estimated median survival in the low- and high-grade groups was 173 and 18 months, respectively. Large size had an unfavorable

Table 2.—Prognostic Factor Analysis for the Rate of Death Due to Disease

effect on tumor-related mortality ($P = .005$), as did colonic site ($P = .006$, Fig 3).

Two unfavorable characteristics were found to have independent prognostic value and were selected in the final Cox model for the rate of death due to the disease: noncurative treatment ($P = .00004$) and high-grade tumor ($P = .0005$). If the curative vs noncurative treatment variable was not considered for inclusion, presentation with metastatic disease

[redacted]

ease ($P = .0001$) and slightly more likely to have a high-grade tumor ($P = .16$). Thus, the prognostic value of tumor size and tumor site disappeared once the effects of presentation with metastatic disease and tumor grade were controlled for ($P > .3$).

Figures 4 and 5 show no prognostic value for tumor size and site among the curatively treated patients ($P > .15$). Tumor mortality curves for tumor grade stratified by type of treat-

[redacted]

Table 5.—Prognostic Factor Analysis for the Rate of Distant Metastasis Among Patients Who Presented With Localized Disease

Unfavorable Characteristic	No. of Patients With Characteristic	Univariable Log-Rank Test, *P**	Score Test *P* Values for Characteristics Selected in Final Cox Model†	Model Coefficient, Mean ± SEM Cox Model
High-grade tumor	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

ment variable was not considered, presentation with metastatic disease and a high-grade tumor were the two unfavorable characteristics that had independent prognostic value. After treatment for localized disease, tumor grade was the only factor found to have a significant association with the rate of development of metastasis. In comparison, in extremity sarcoma, both tumor grade and size have been found to be independent prognosticators for the rates of development of metastasis and tumor mortality.[18]

Another important finding in this study was that, once distant metastases had occurred, none of the variables measured at initial presentation, such as tumor grade, tumor size, tumor location, age, or sex, affected survival after metastasis. Moreover, there is no difference in survival after metastasis between patients who initially presented with metastases and those who developed a distant recurrence following resection with curative intent. In patients with low-grade tumors, recurrence was noticed even after 15 years of follow-up. This slow, indolent clinical course, followed by late recurrence and subsequent death due to the disease, has also been noted with leiomyosarcomas at other sites.[11] Liver metastasis developed in one of our patients 17 years after the initial diagnosis.

The clinical presentation of intestinal leiomyosarcoma as an inflammatory process has been previously described.[2,8] Each of the four patients in our study with an inflammatory condition had a large tumor with extensive necrosis, cavitation, and, in one case, fistula formation, and all four died of the disease.

Regional lymph node metastasis occurred in at least six of our 50 patients; if we omit patients who underwent only biopsy or local excision (in these cases no regional lymphadenectomy was performed), six (21%) of 29 patients had metastases. Four of these six patients had metastatic disease at the time of operation, and all six patients had a high-grade sarcoma. Akwari et al[9] reported an incidence of 6% in their series of 108 cases of leiomyosarcoma of the small and large bowel. The aforementioned low figures of colorectal lymph node metastasis are in accordance with the occurrence of lymph node metastasis in sarcoma of the extremity.[18] Our data clearly show that colorectal leiomyosarcoma predominantly spreads to the liver and peritoneal cavity. Lung metastasis was relatively rare. A similar pattern was observed by Akwari et al.[9] The predominant occurrence of liver metastasis compared with the low incidence of lung metastasis can be explained by tumor cells invading the portal circulation. The hematogenous metastatic spread of colorectal sarcomas resembles that of large-bowel carcinomas. However, this mode of spread is different from that in extremity sarcoma, in which the dominant site of metastasis is the lung. This is probably due to the difference in venous drainage between large-bowel and extremity sarcomas.

In several of our cases, implants on peritoneum and omentum were extensive. This peritoneal seeding resembles the intra-abdominal spread of ovarian cancer and is in contrast to the behavior of most colorectal carcinomas. A possible explanation for this pattern of spread might be the intramural localizations of leiomyosarcoma in the bowel wall itself. Invading and traversing the one-layer peritoneum can occur at an early stage.

The extent of operation had no effect on patient outcome. The surgical treatment of choice in colorectal sarcoma appears to be similar to that for sarcomatous tumors at other sites, namely, radical local excision with a margin of normal uninvolved tissue to ensure complete extirpation. For tumors larger than 5 cm in the rectal region, this often means an abdominoperineal resection. Limited or palliative resections did not appear to offer greater benefit to the patient than biopsy only.

Current data are in conflict concerning the role of adjuvant chemotherapy for soft-tissue sarcoma. Although no benefit has been demonstrated for retroperitoneal sarcomas,[19,20] some studies have shown an advantage for extremity sarcomas.[21,22] Our experience with adjuvant chemotherapy in colorectal sarcomas is limited, and in view of the rarity of colorectal sarcoma, a prospective study to question the role of adjuvant chemotherapy would be difficult to achieve.

In summary, the most important prognostic factor in localized colorectal sarcoma is tumor grade. Metastatic spread occurs primarily to the liver and peritoneal cavity and, to a far lesser extent, the lungs. Surgery is currently the only curative mode of therapy. Local radical excision is recommended, since the definite roles of radiotherapy and chemotherapy are not yet established.

This study was supported in part by grant CA47179 from the National Institutes of Health (Dr Brennan).

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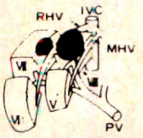
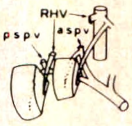
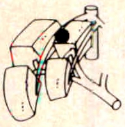
Primary Colorectal Sarcoma—Meijer et al

BLOOD SWEAT

[redacted]

Patient No./ Sex/Age, y	Tumor-Occupied Segment Size, cm*	Operative Procedure	Questionable Segment After Operation Drainage Vein
1/M/61	S_7 4×3×3 S_8 7×8×7 	 S_7,S_8 Resection With Proximal RHV Sacrifice	S_6 RIHV
2/M/67	S_8 2×2×2.5 		
3/M/60	S 3.5×4×4		

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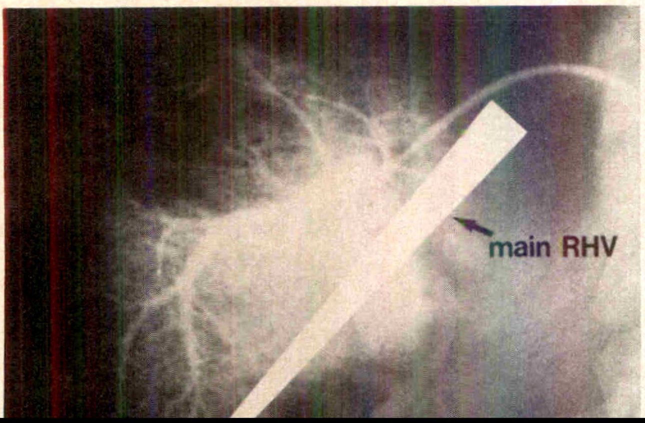
Clinical Findings and Prognosis

Case No.	Liver Cirrhosis	Child's Classification	Findings That Made Our Procedures Necessary*	Type of Resection	Final Outcome
1	Positive	B	Invasion to proximal RHV	Noncurative	Alive for 2 y 7 mo
2	Positive	B	Invasion to proximal RHV	Curative	Died of cirrhosis after 9 mo
3	Positive	B	Displacement of proximal RHV	Curative	Alive for 8 mo
4	Positive	A	Small daughter nodules around proximal RHV	Curative	Alive for 3 y 4 mo
5	Negative†	A	Displacement of proximal RHV	Noncurative	Alive for 9 mo
6	Positive	B	Small daughter nodules around proximal RHV	Curative	Alive for 1 y 9 mo
7	Positive	A	Displacement of distal RHV	Curative	Alive for 7 mo
8	Positive	A	Displacement of proximal MHV	Noncurative	Alive for 9 mo
9	Positive	A	Displacement of proximal MHV	Curative	Alive for 11 mo

*RHV indicates right hepatic vein; MHV, middle hepatic vein.
†Chronic active hepatitis.



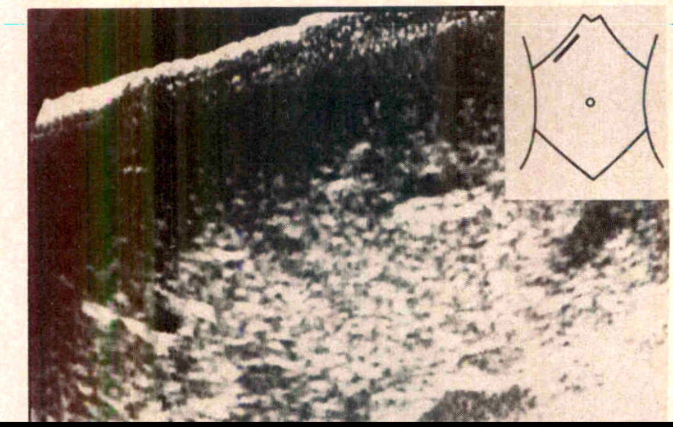


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Figure 4 shows RIHV of case 1, the drainage type of which is regarded as average by Couinaud,[9] and will be described below.

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drained by RHV, we can expect the development of collater-

[redacted]

III, ed. *The Liver and Portal Hypertension*. Philadelphia, Pa: WB Saunders

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outflow obstruction, however, showed subtotal necrosis and no abscess formation. A possible explanation is that flaps with venous obstruction have more severe deficiencies of tissue oxygenation and are unable to wall off the offending organisms, leading to increases in bacterial counts and tissue death.

We have shown that venous obstruction potentiates distal necrosis in infected island skin flaps, resulting from the inability of the host to mount a sufficient defense when faced with a structurally and biochemically inefficient local environment. Early correction of venous compromise may prevent the poor perfusion that leads to the structural and metabolic derangements that have been seen here to raise bacterial counts, promote distal flap necrosis, and prevent defensive abscess formation by the host. Interestingly, McGrath[27] has reported increased flap survival when flaps were treated with topical silver sulfadiazine. It follows that if relative obstruction cannot be relieved, it may be worthwhile to treat a flap with topical antibacterials to prevent the additive effect of bacteria and obstruction.

References

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Duplex Imaging and Incidence of Carotid Radiation Injury After High-Dose Radiotherapy for Tumors of the Head and Neck

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before scanning had moderate or severe carotid disease when examined by duplex scanning, a fivefold higher incidence than in the 38 patients in the nonirradiated group. A similar finding in patients who did not undergo irradiation was reported by Colgan et al,[21] who with duplex scanning observed a 5% incidence of 50% or greater diameter stenoses among 348 unselected patients at health fairs. Although the incidence of moderate or severe disease vs time did not increase in a statistically significant manner, the number of patients undergoing irradiation who were followed up for long periods irradiation over a longer time is clearly needed to provide more definitive information on the natural history of such lesions. Moreover, because the number of patients given chemotherapy protocols was small, any conclusions on the influence of chemotherapy must be considered preliminary. Because the prevention of stroke is the primary reason to perform carotid endarterectomy, surgical intervention in this group of patients may be justified in the presence of severe preocclusive or symptomatic lesions. As the difficulty and risk of operation are greater in the fibrotic, previously irradi-

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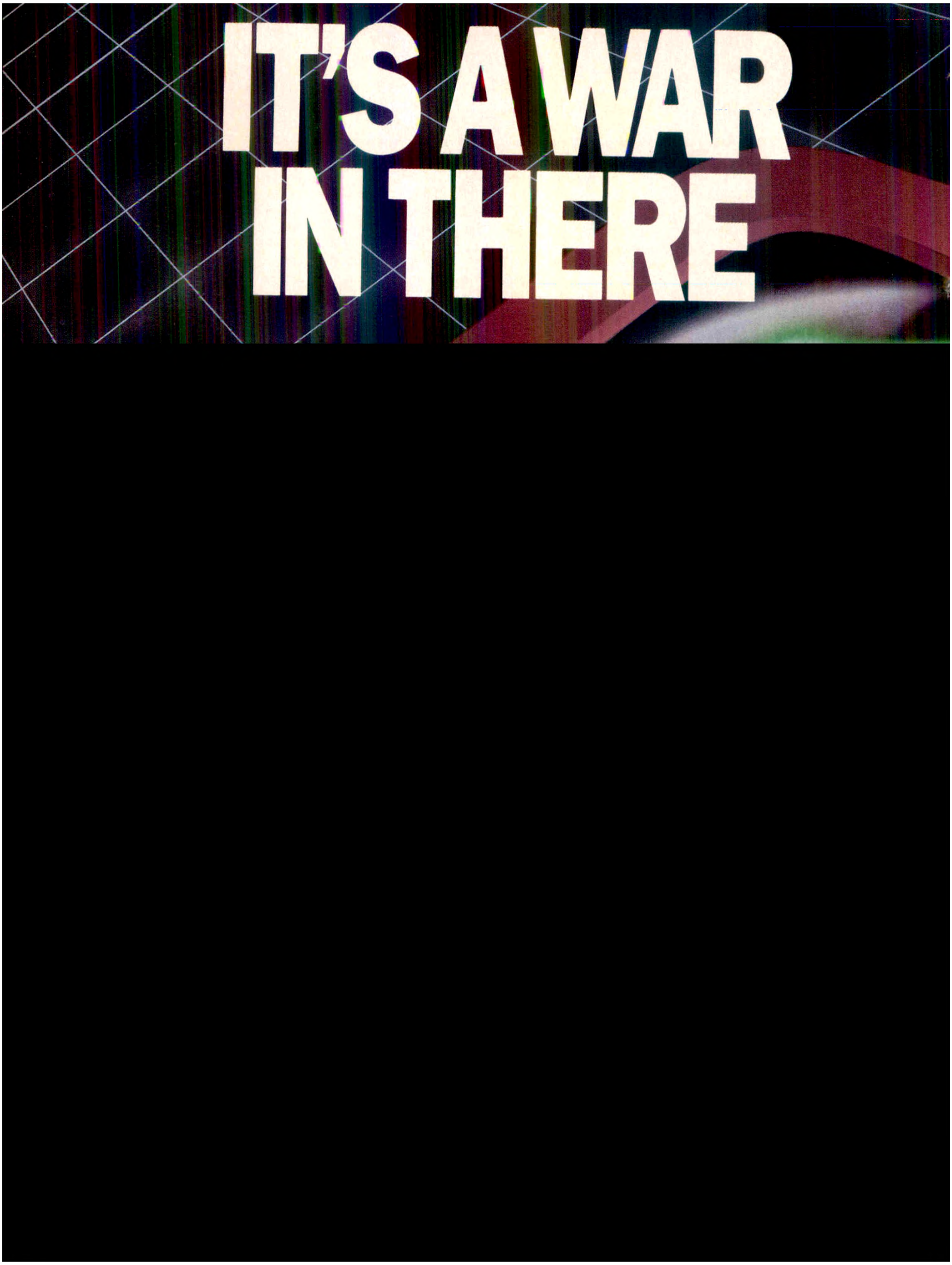
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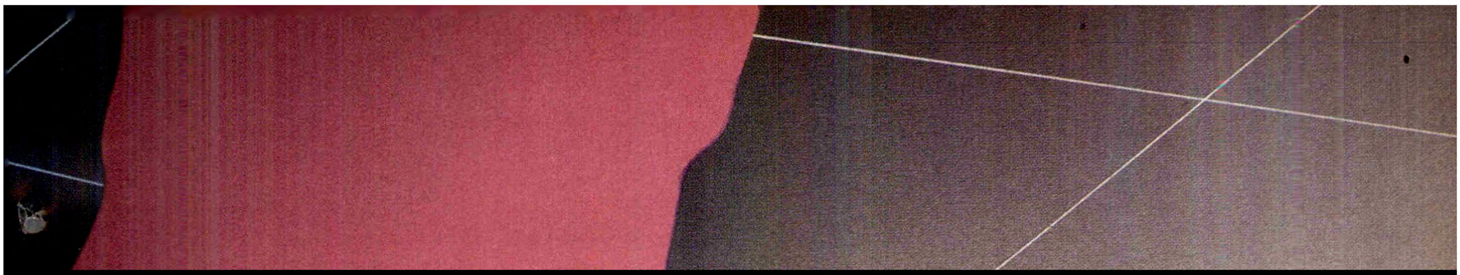

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MEZLIN IV/IM

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fluid in the pericardium. Tympany may be elicited on percussion.[5]

Due to the close anatomic relationship between the heart and the pericardium, it is very likely that a pericardial breach is associated with an underlying myocardial injury. We found pneumopericardium in 15% of the chest roentgenograms of

The natural history of patients with small blood collections in the pericardium is not known. No cases of late constrictive pericarditis have been reported, to our knowledge. Two of our patients with blood in the pericardium were followed up for 10 and 18 months after the injury and were asymptomatic.

The mere presence of air in the pericardium usually has no

[redacted]

Effective ***Staph*** *Reduction*

ZINACEF® IM/IV GLAXO

sterile cefuroxime sodium

- ☐ Outstanding protection against postsurgical staphylococcal infections[1]
- ☐ More effective surgical prophylaxis* than cefazolin[1,2]
- ☐ Beta-lactamase stability superior to cefazolin[2]
- ☐ More convenient, economical dosing than cefazolin[3]

*In clean-contaminated or potentially contaminated surgical procedures.

For a complete listing of indications and usage, please consult Brief Summary of Prescribing Information for ZINACEF on adjacent page.

Glaxo Pharmaceuticals™
DIVISION OF GLAXO INC.
Research Triangle Park, NC 27709

Zinacef®
(sterile cefuroxime sodium, Glaxo)

Zinacef®
(cefuroxime sodium injection)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zinacef® product labeling.

INDICATIONS AND USAGE: Zinacef® is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

1. **Lower Respiratory Tract Infections,** including pneumonia, caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*), *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* spp, *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing), *Streptococcus pyogenes*, and *Escherichia coli*.
2. **Urinary Tract Infections** caused by *E coli* and *Klebsiella* spp.
3. **Skin and Skin Structure Infections** caused by *S aureus* (penicillinase- and non-penicillinase-producing), *S pyogenes*, *E coli*, *Klebsiella* spp, and *Enterobacter* spp.
4. **Septicemia** caused by *S aureus* (penicillinase- and non-penicillinase-producing), *S pneumoniae*, *E coli*, *H influenzae* (including ampicillin-resistant strains), and *Klebsiella* spp.
5. **Meningitis** caused by *S pneumoniae*, *H influenzae* (including ampicillin-resistant strains), *Neisseria meningitidis*, and *S aureus* (penicillinase- and non-penicillinase-producing).
6. **Gonorrhea:** Uncomplicated and disseminated gonococcal infections due to *Neisseria gonorrhoeae* (penicillinase- and non-penicillinase-producing strains) in both males and females.

[redacted]

NOW: REASON TO REFER

[redacted]

ERGAMISOL® (Levamisole Hydrochloride) Tablets

Before prescribing, please consult complete prescribing information of which the following is a brief summary.

INDICATIONS AND USAGE: ERGAMISOL (levamisole hydrochloride) is only indicated as adjuvant treatment in combination with fluorouracil after surgical resection in patients with Dukes' stage C colon cancer.

CONTRAINDICATIONS: ERGAMISOL (levamisole hydrochloride) is contraindicated in patients with a known hypersensitivity to the drug or its components.

WARNINGS: ERGAMISOL (levamisole hydrochloride) has been associated with agranulocytosis, sometimes fatal. The onset of agranulocytosis is frequently accompanied by a flu-like syndrome (fever, chills, etc.); however, in a small number of patients it is asymptomatic. A flu-like syndrome may also occur in the absence of agranulocytosis. It is essential that appropriate hematological monitoring be done routinely during therapy with ERGAMISOL and fluorouracil. Neutropenia is usually reversible following discontinuation of therapy. Patients should be instructed to report immediately any flu-like symptoms.

Higher than recommended doses of ERGAMISOL may be associated with an increased incidence of agranulocytosis, so the recommended dose should not be exceeded.

The combination of ERGAMISOL and fluorouracil has been associated with frequent neutropenia, anemia and thrombocytopenia.

PRECAUTIONS: Before beginning this combination adjuvant treatment, the physician should become familiar with the labeling for fluorouracil.

Adverse experience	**ERGAMISOL N = 440 %**	**ERGAMISOL plus fluorouracil N = 599 %**
Gastrointestinal		
Nausea	22	65
Diarrhea	13	52
Stomatitis	3	39
Vomiting	6	20
Anorexia	2	6
Abdominal pain	2	5
Constipation	2	3
Flatulence	<1	2
Dyspepsia	<1	1
Hematological		
Leukopenia		
<2000/mm³	<1	1
≥2000 to <4000/mm³	4	19
≥4000/mm³	2	33
unscored category	0	<1
Thrombocytopenia		
<50,000/mm³	0	0
≥50,000 to <130,000/mm³	1	8
≥130,000/mm³	1	10
Anemia	0	6
Granulocytopenia	<1	2

[redacted]

[redacted]

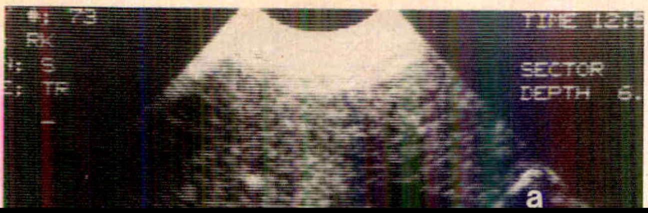

Table 5.—Extrarenal Thrombosis

	Group 1A	Group 1B	Group 2 (A and B)
Inferior vena cava	6	3	4
Pulmonary embolus	. . .	2	5
Splenic/hepatic veins	. . .	1	2

[redacted]

There is no proved advantage of early nephrectomy or thrombectomy, even with bilateral involvement, as demonstrated in this review. Many of the described patients (including one patient in our series) were operated on after the acute phase

[redacted]

reported survival rates, which range between 45% and 86%.[25-27] In surviving patients, the renal venous thrombosis occurs as a complication of an otherwise mild or moderate illness, leading to recognition during life. This includes most

The KTP/YAG
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More laparoscopic cholecystectomies have been performed with the KTP/YAG™ Surgical Laser System from Laserscope® than with any other laser or non-laser dissecting instrument. General surgeons now have a single tool optimized for bloodless dissection of the gallbladder with minimal complications.

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[redacted]

Surgical History

[redacted]

XXIV.

Ueber die operative Behandlung der Embolie der Lungenarterie.[1])

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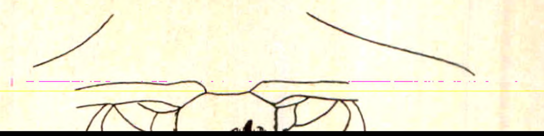

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telephone at my home, at a distance of 8 minutes' travel. The operation took 5 minutes from incision to opening of the pulmonary artery, in spite of being delayed and made more difficult by old adhesions between the lung and pleura.

By opening the left pleural space, the surgeon was subjecting the patient to the additional handicap of open pneumothorax, which, under open-drop anesthesia, was itself likely to be lethal. Only 4 years had passed since Ferdinand Sauerbruch of Breslau and Ludolph Brauer of Heidelberg had described their Unterdruck and Überdruck chambers for assistance of spontaneous ventilation with patients under anesthesia and in

longest of which was 15 cm, and the patient eventually made a full recovery.

Only scattered reports of successful outcomes were published from around the world during the next three decades. Successful embolectomy by the Trendelenburg method was first reported in the United States by R. W. Steenburg, MD, and Richard Warren, MD, from the (then) Peter Bent Brigham Hospital, Boston, Mass, in 1958.[6] Cardiopulmonary bypass was becoming available and seemed to promise much better control, but at the time it still was not easily adaptable to emergency use. Successful embolectomies were accom-

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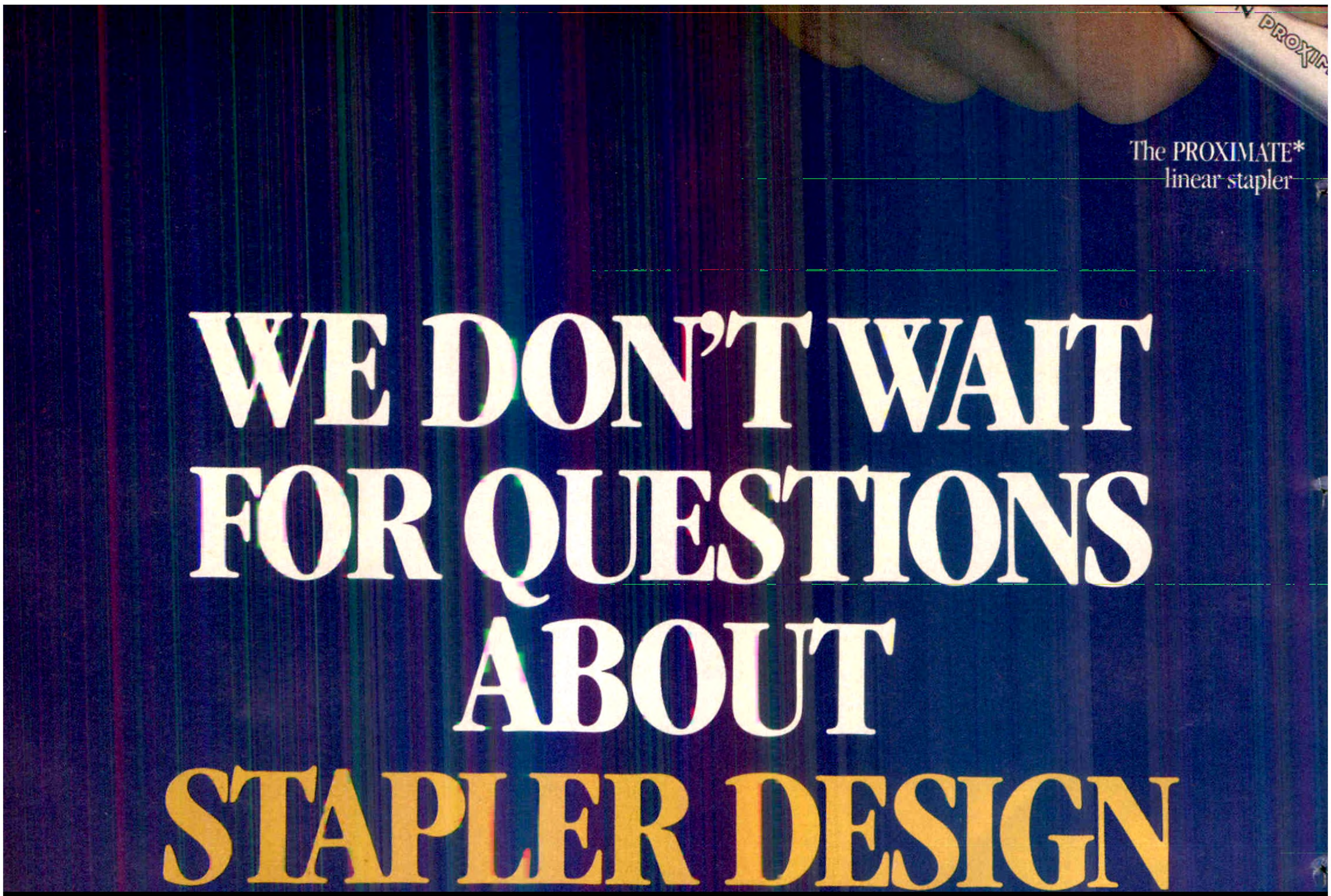
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ABOUT
STAPLER DESIGN

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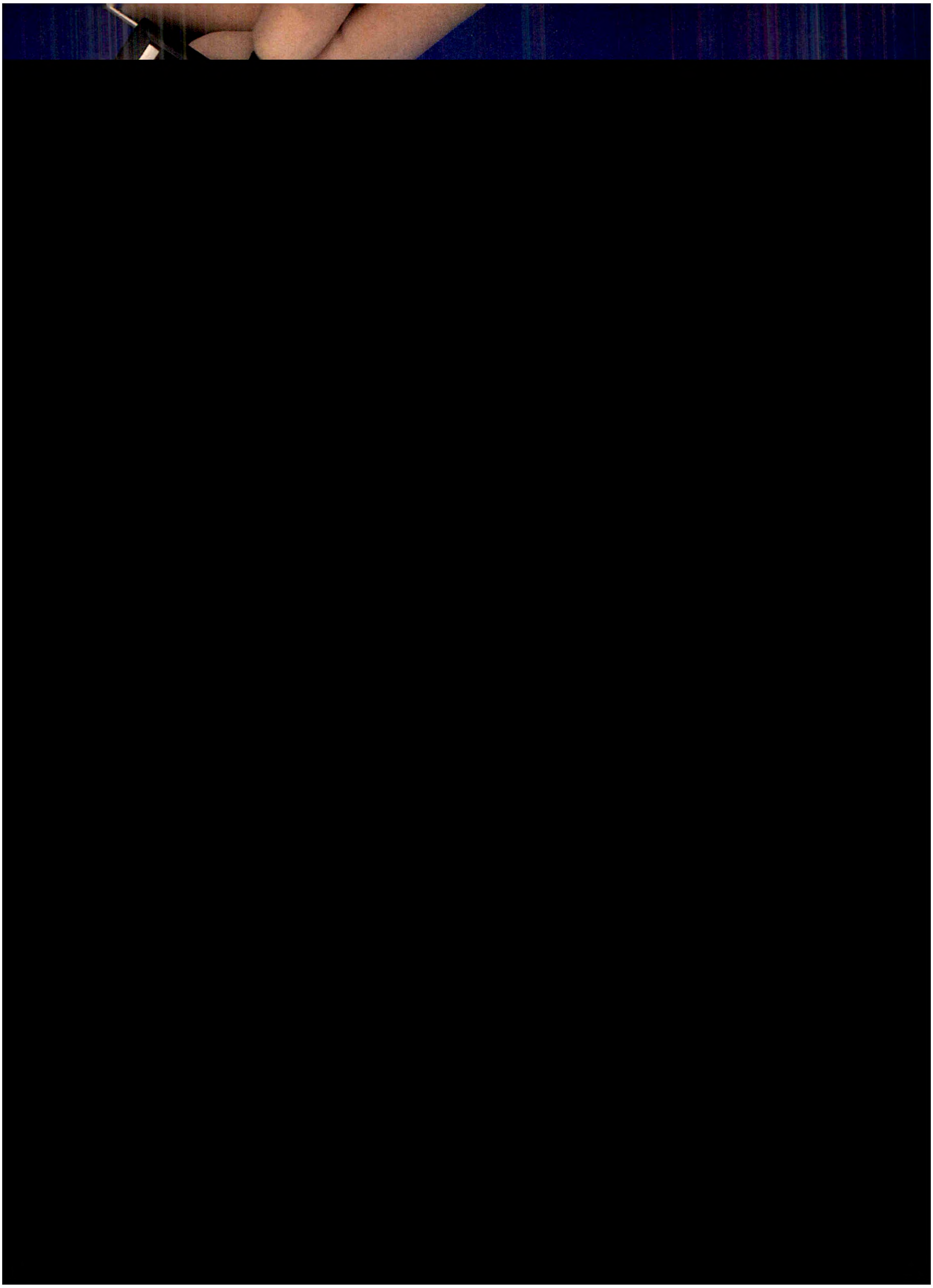

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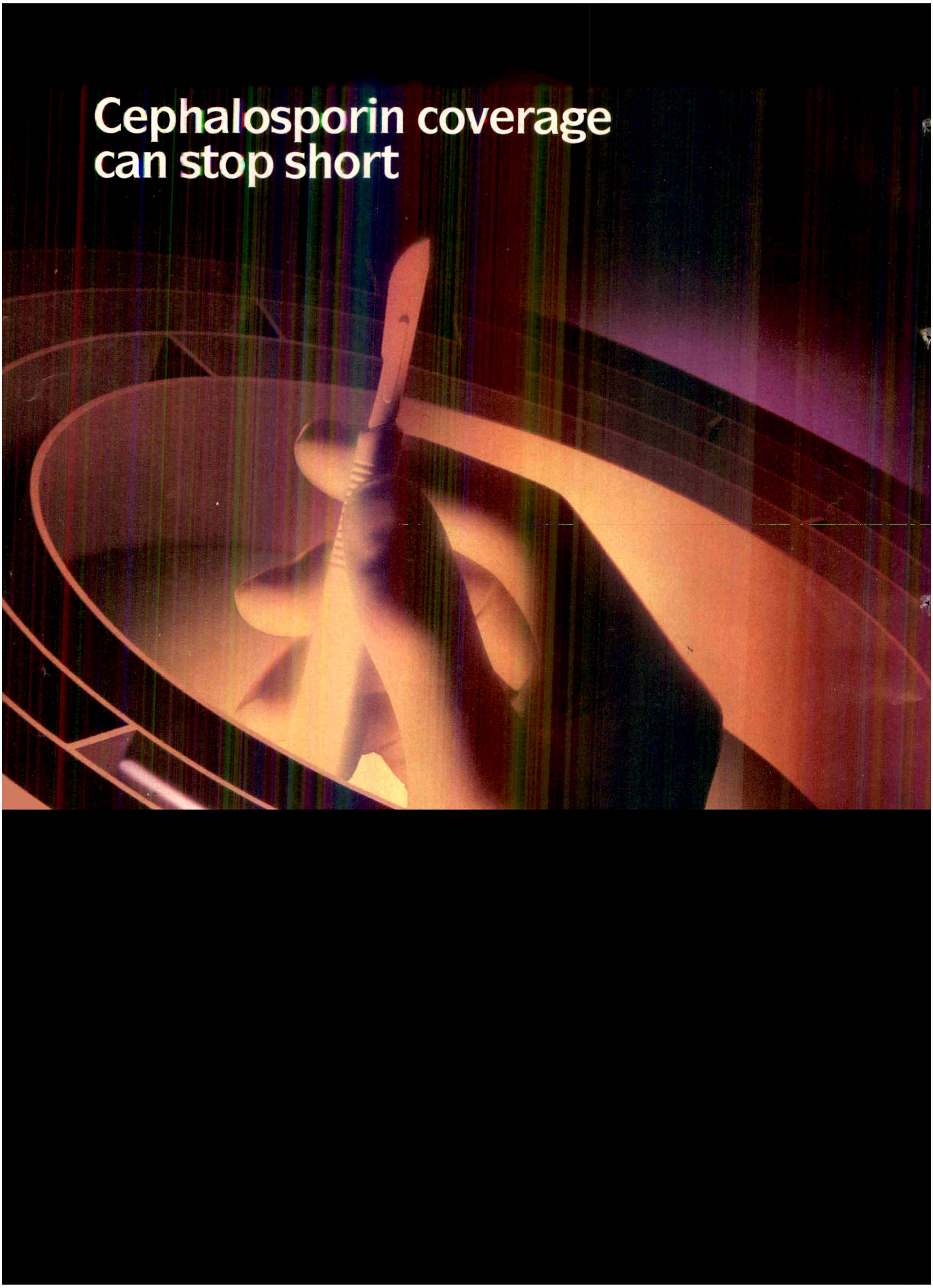

Cephalosporin coverage can stop short

[redacted]

BRIEF SUMMARY OF PRESCRIBING INFORMATION

TIMENTIN® **sterile ticarcillin disodium and clavulanate potassium** for Intravenous Administration

INDICATIONS AND USAGE: TIMENTIN® is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Bacterial Septicemia: including bacteremia, caused by ß-lactamase

Encouragement

[redacted]

[redacted]

Table 2.—Biologic Findings*

Patient No.	AST, U/L	ALT, U/L	GGT, U/L	Alkaline Phosphatase, U/L	Bilirubin, μmol/L

[redacted]

Nitrogen Embolus as a Complication

[redacted]

Cystic Teratomas of the Pancreas

Marcelo Mester, MD; Hersz J. Trajber, MD; Carolyn C. Compton, MD, PhD; Helio S. A. de Camargo, Jr, MD;
Paulo C. Cardoso de Almeida, MD; Herbert C. Hoover, Jr, MD

• Cystic teratomas of the pancreas constitute an extremely rare entity with only nine cases, to our knowledge, described in the world literature. Symptoms are usually due to the compressive effects of the tumor on the neighboring organs. They should be considered in the differential diagnosis of slow-growing benign pancreatic cysts. We describe a 25-year-old woman with a pancreatic teratoma who was operated on in 1976 with the diagnosis of calcified pancreatic cyst. The diagnostic and surgical procedures are described, as well as a 14-year follow-up. The previously published cases are reviewed and the differential diagnosis is discussed. Early diagnosis and the need for total tumor resection are emphasized.

(*Arch Surg.* 1990;125:1215-1218)

The correct diagnosis and management of pancreatic cysts are important issues for the surgeon.[1] The risk of overlooking malignancy or misdiagnosing true cysts as pseudocysts may have serious consequences for the patient. The differential diagnosis between slow-growing benign cysts and their malignant counterparts is often difficult.[2] Thus, both the benign and the malignant forms of the disease may be treated at an advanced stage when curative resection of malignancy is not attainable, or when significant adherence to vital structures in the benign cysts changes the extent and risk of the operation.[3,4] Cystic teratomas of the pancreas are no exception to this concept. As benign extragonadal germ cell tumors, cystic teratomas are usually seen in the younger population. There are no easy clues for their preoperative recognition but current imaging methods, such as ultrasonography or computed tomography, may be helpful.

We describe only the 10th reported case of pancreatic teratoma and review the 9 previously published cases. The difficulties and limitations of diagnosis as well as surgical alternatives are discussed. Emphasis is placed on early recognition, differential diagnosis from malignant cysts, and the need for radical excision of the tumor mass.

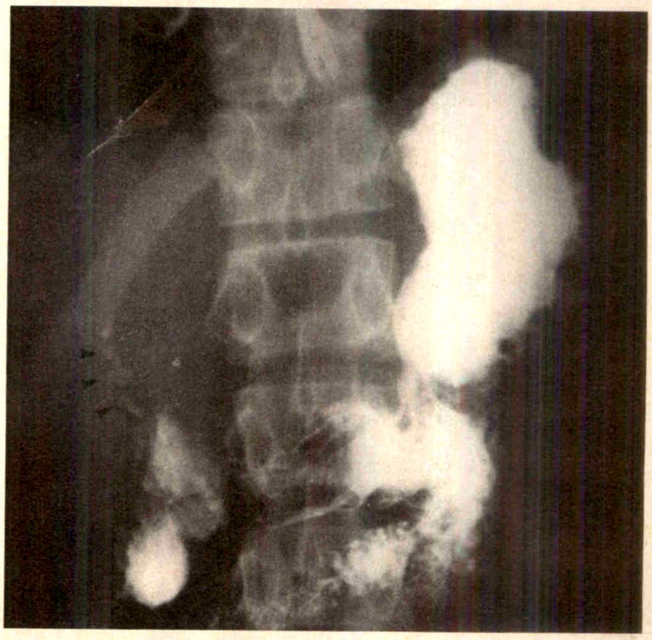
REPORT OF A CASE

A 25-year-old white woman born in São Paulo, Brazil, presented with a 3-year history of crampy right upper quadrant abdominal pain. The pain was not related to food ingestion and was frequently followed by nausea and vomiting. Pain relief was obtained with antispasmodics and tranquilizers. The patient denied episodes of fever, chills, or jaundice and had experienced no weight loss. Her past history was significant only for bronchial asthma.

The patient was in good general health with essentially normal physical examination results except for tenderness in the right upper quadrant and a palpable liver 1 cm below the right costal margin. Results of laboratory tests (complete blood cell count, blood chemistries, urinalysis) were within normal limits. An oral cholecystogram showed normal gallbladder function. An upper gastrointestinal tract roentgenographic series showed a normal stomach and duodenum, but calcifications in the right upper quadrant of the abdomen were visualized (Fig 1). Both kidneys and ureters were normal on intravenous pyelogram. However, a cyst with mural calcifications and densely calcific contents was seen in the right hypochondrium. Intravenous cholangiography disclosed a lateral dislocation with downward elongation of the common bile duct and upward displacement of the gallbladder (Fig 2).

The patient underwent an exploratory laparotomy with the preoperative diagnosis of calcified pancreatic cyst. A cystic tumor 8 cm in

Fig 1.—Upper gastrointestinal roentgenographic series of our patient showing a calcified mass extrinsic to the stomach and duodenum (arrowheads).

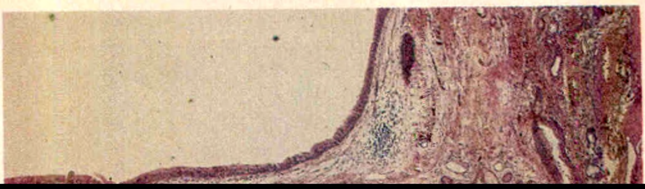


Accepted for publication March 31, 1990.

From the Departments of Surgery (Drs Mester and Hoover) and Pathology (Dr Compton), Massachusetts General Hospital, Harvard Medical School, Boston; GI Surgery Unit, Municipal Hospital, São Paulo, Brazil (Dr Trajber); and the Departments of Pathology (Dr Cardoso de Almeida) and Gynecology (Dr de Camargo), University of São Paulo. Dr de Camargo is now in private practice.

Reprint requests to Division of Surgical Oncology, Massachusetts General Hospital, Boston, MA 02114 (Dr Mester).

Cystic Teratomas—Mester et al 1215



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Review of Cystic Teratomas of the Pancreas

Source, y	Age, y/Sex	Symptoms	Physical Examination	Preoperative Diagnosis	Surgical Findings	Procedure	Follow-up
Kerr,[15] 1918	55/F	"Indigestion"	Palpable tumor	Abdominal mass	Cystic tumor in head of pancreas	Drainage	Partial tumor resection and drainage 2 mo later
Judd,[27] 1921	33/F	Lumbar pain	Palpable tumor	Pancreatic cyst	Cystic tumor in tail of pancreas	Resection	Cholecystectomy after 2 y

[redacted]

hypochondria. The tumors were variably described as mobile or fixed, firm or cystic, smooth or nodular and were found in the head, body, or tail of the pancreas. The majority contained mucus and hair within the cyst cavity.

Operative therapy of the reported cases has included both tumor resection and external drainage of the cyst. In one unusual situation, the superior mesenteric vein was ligated and a two-stage operation was carried out due to the size of the cyst and local bleeding during dissection.[3] Only one of the

sity through transmission, and solid inhomogeneous areas with acoustic shadowing. Computed tomography may further define small loculations with sharp interfaces and calcifications. If a biopsy is attempted, the findings of a well-defined cystic wall lined by columnar epithelium with a dense stroma would be consistent with a mucinous cystic neoplasm, either benign or malignant.[16] Papillary-cystic neoplasms will have solid masses and papillary structures interspersed with necrosis and hemorrhage.[19,20] Ultrastructurally, it is possible to

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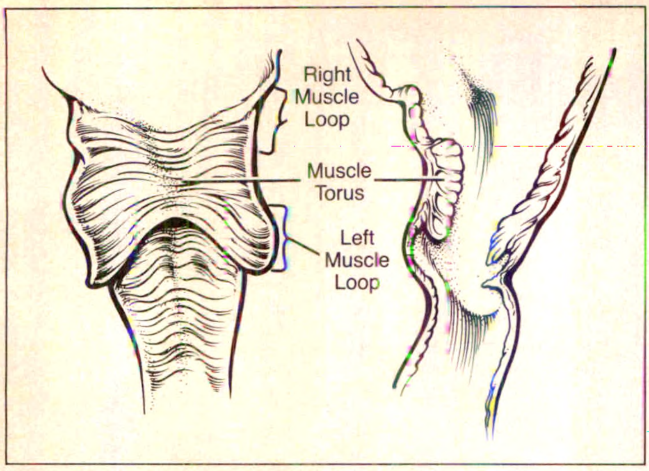

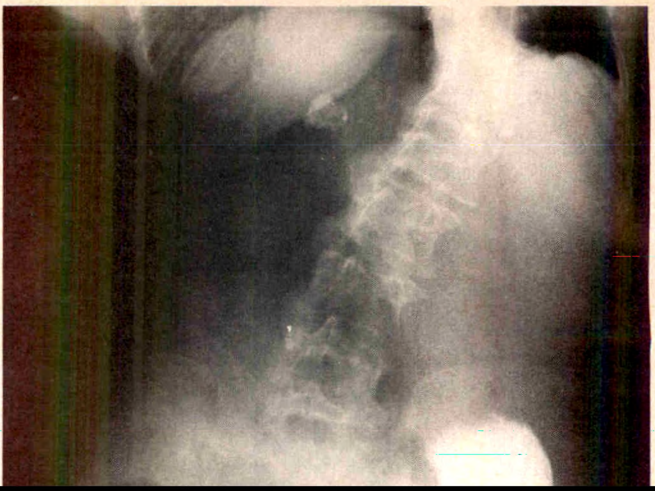

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avity at the junction of the right atrium and the IVC helps to irect the tip of the insertion device into the IVC. Fluoroscoy is used to direct the catheter to the confluence of the ommon iliac veins. An inferior venacavogram is then obained to delineate caval anatomy by injecting a 30-mL bolus

[redacted]

successful insertion of a Mobin-Uddin umbrella in four patients in conjunction with pulmonary embolectomy. The umbrella was positioned using a renal pyelogram to estimate the location of the renal veins. Wellon[3] placed a Mobin-Uddin umbrella transatrially in two patients at the time of pulmo-

Correspondence and Brief Communications

A Plea for Role Models

To the Editor.—Ward Griffen's com-

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plants regenerate, and that there is a negative correlation between the num-

an experimental procedure which cannot be reliably performed in humans if one's intent is to protect the recipi-

Legends.—*Legends* must be typed double-spaced, beginning on a separate sheet of paper. Length is limited to a maximum of 40 words.

Tables.—Each table must be typed double-spaced, including all headings, on a separate sheet of 8½ × 11-in paper. Do not use larger-size paper. If a table must be continued, use a second sheet and repeat all heads and stubs. Each table must have a title.

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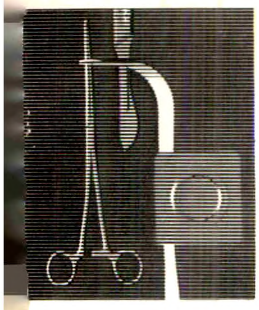

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CEFOTAN® IM/IV
(cefotetan disodium)

In intra-abdominal and gynecologic infection due to indicated organisms

For Intravenous or Intramuscular Use
BRIEF SUMMARY

INDICATIONS AND USAGE
TREATMENT: CEFOTAN® (cefotetan disodium) is indicated for the therapeutic treatment of the following infections when caused by susceptible strains of the designated organisms:
Urinary tract infections caused by *E coli, Klebsiella* species (including *K pneumoniae*), *Proteus mirabilis* and *Proteus* sp (which may include the organisms now called *Proteus vulgaris, Providencia*

developmentally analogous to late childhood and prepuberty in humans) resulted in reduced testicular weight and seminiferous tubule degeneration in 10 of 10 animals. Affected cells included spermatogonia and spermatocytes; Sertoli and Leydig cells were unaffected. Incidence and severity of lesions were dose-dependent; at 120 mg/kg/day (approximately 2-4 times the usual human dose) only 1 of 10 treated animals was affected, and the degree of degeneration was mild.

Similar lesions have been observed in experiments of comparable design with other methylthiotetrazole-

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+ **more cost-effective than cefoxitin**[1,2]

− **less frequent dosing than cefoxitin**[3,4]

× **several times the half-life of cefoxitin**[5,6]

÷ **single-dose prophylaxis/ twice-daily treatment**

31 OCT 1990

Count on

CEFOTAN® IM/IV

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In intra-abdominal and gynecologic infection due to indicated organisms

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Please see adjacent page for brief summary of prescribing information.